

IDENTIFICATION OF NOVEL BIOMARKERS IN OVARIAN CANCER: SYSTEMS BIOLOGY APPROACHES

ESRA GÖV

© Copyright 2020

Printing, broadcasting and sales rights of this book are reserved to Akademisyen Publishing House Inc. All or parts of this book may not be reproduced, printed or distributed by any means mechanical, electronic, photocopying, magnetic paper and/or other methods without prior written permission of the publisher. Tables, figures and graphics cannot be used for commercial purposes without permission. This book is sold with banderol of Republic of Turkey Ministry of Culture.

ISBN

978-605-258-831-4

Book Title

Identification Of Novel Biomarkers In Ovarian Cancer:
Systems Biology Approaches

Author

Esra GÖV

Publishing Coordinator

Yasin Dilmen

Page and Cover Design

Typesetting and Cover Design by Akademisyen

Publisher Certificate Number

25465

Printing and Binding

Printing press Soncqag Matbaacilik

Bisac Code

SCI010000

GENERAL DISTRIBUTION

Akademisyen Kitabevi A.Ş.

Halk Sokak 5 / A

Yenişehir / Ankara

Tel: 0312 431 16 33

siparis@akademisyen.com

www.akademisyen.com

ACKNOWLEDGEMENT

My graduate studies would not have been possible without the support of many people. Words cannot describe my gratitude for everyone who has encouraged and helped me along the way. Firstly, I would like to thank Dr. Kazım Yalçın Arga, my thesis advisor, for allowing me the opportunity to work in his research group. I am greatly appreciative for his teaching, training, and advice. His advices on both research and on my academic career have been invaluable. I would also like to extend my appreciation to the Examination Committee members, Dr. Halime Kenar and Dr. Berna Sarıyar Akbulut. Besides, Dr. Kenar who was co-advisor of my master thesis, is special for me in all respects.

The financial support by Marmara University, Scientific Research Projects Committee (BAPKO) through project FEN-C-DRP-110915-0445 is gratefully acknowledged. Thank you to all past and present members of the Arga's lab. I am deeply grateful to my lifelong support network of friends, both near and far. Especially, thank you Medi Kori, Dilara Ayyıldız, Büşra Aydın and Beste Turanlı for just everything, I love you girls.

A special thanks to my precious family members, mum, sister and brother. They have also helped me maintain my sense of humor and mental equilibrium. Lastly, my family- husband and son, R. Fatih Göv and A. Gökberk Göv, whom I love very much, thank you for your endless love, support and encouragement. I would not have made it without you.

CONTENTS

Acknowledgement.....	iii
Abbreviations	xi
1. Introduction	1
1.1. RNA-based ovarian cancer research	3
1.1.1. RNA expression profiling in ovarian cancer	3
1.1.2. Expression profiling of microRNAs	11
1.1.3. Ovarian cancer associated signaling pathways	13
1.1.4. Integrative approaches in ovarian cancer research..	16
1.2. Ovarian cancer research should meet integrative multi-omics science	18
1.2.1. Human transcriptional regulatory network.....	23
1.2.2. Integration of transcriptome data with biological networks.....	27
1.2.3. Differential co-expression network in ovarian cancer.....	28
1.2.4. Differential interactome in ovarian cancer.....	29
1.3. Ovarian diseases including polycystic ovarian syndrome (PCOS), ovarian endometriosis and ovarian cancer.....	30
1.4. Aim of the Study	34
2. Materials and Methods	35
2.1. Reconstruction of transcriptional regulatory network of <i>H. sapiens</i>	35
2.2. Topological analysis of transcriptional regulatory networks	36
2.3. Selection of gene expression datasets.....	38
2.4. Identification of differentially expressed genes.....	39
2.5. Reconstruction of ovarian cancer specific subnetwork....	42
2.6. Analysis of network performance	42
2.7. Robustness analysis	43

2.8. Identification of reporter receptors, membrane proteins, transcription factors and miRNAs	43
2.9. Determination of reporter metabolites.....	44
2.10. Enrichment analyses of DEGs and reporter metabolites	44
2.11. Comprehensive networks in CEPI, stroma and tumor tissues	44
2.12. Construction of co-expression networks in diseased and healthy states	45
2.13. Determination of network modules and their differential co-expression.....	45
2.14. Prognostic power analysis of module genes.....	46
2.15. Identification of transcriptional regulatory network including module genes.....	46
2.16. Screening the differential expression of the module in different tumor types	46
2.17. Differential Protein Interactome Analysis.....	47
2.17.1. Protein interaction data	47
2.17.2. Determination of entropies corresponding to each interaction	47
3. Results and Discussion.....	51
3.1. A generic transcriptional regulatory network of <i>H. sapiens</i> was reconstructed	51
3.1.1. The network motifs provide a deeper investigation into the topological architecture	57
3.1.2. Core network topology endorses the previous findings on miRNA and gene interactions	60
3.1.3. Target genes may be regulated in cooperation of regulators.....	64
3.1.4. A target gene may be regulated by multiple upstream effectors in a hierarchical operation.....	65
3.1.5. Process-specific subnetworks were also dominated by hierarchical operation of regulators.....	67

3.1.6. Ovarian cancer specific transcriptional regulatory network	68
3.2. Reporter biomolecules of ovarian cancer were identified through network medicine perspective	71
3.2.1. Transcriptomic signatures of ovarian CEPI, stroma and tumor tissues.....	72
3.2.2. Signaling receivers: reporter receptors and membrane proteins.....	74
3.2.3. Regulatory signatures: reporter transcription factors and microRNAs.....	76
3.2.4. Metabolomic signatures: reporter metabolites	78
3.2.5. Biological insights of transcriptomic signatures and reporter metabolites.....	81
3.2.6. Tissue specific comprehensive networks with enriched reporter biomolecules	83
3.3. Differential co-expression analysis reveals a novel prognostic gene module in ovarian cancer.....	85
3.3.1. Differential gene expression in ovarian cancer.....	85
3.3.2. Co-expression profiles in ovarian cancer	87
3.3.3. Co-expressed gene modules in diseased and healthy states.....	88
3.3.4. The module was differentially co-expressed in ovarian cancer	91
3.3.5. Prognostic performance of the gene module.....	99
3.3.6. Transcriptional regulators of the module genes ...	100
3.3.7. Differential expression of the module genes in different tumor types.....	101
3.4. Ovarian cancer differential interactome and network entropy analysis reveal new candidate biomarkers.....	104
3.4.1. DNA repair responses	105
3.4.2. Alternative splicing mechanisms and abnormal protein expression in tumor cells.....	106
3.4.3. Separation of sister chromatids through ESPL1 ...	106

3.4.4. Suppression of EGFR-associated proliferation via EGFR endocytosis and retinoids	107
3.4.5. Nucleocytoplasmic translocation of estrogen receptor in ovarian cancer	107
3.4.6. Cellular response to malignancies.....	108
3.5. Integrative and comparative analysis of ovarian diseases point out molecular signatures.....	112
3.5.1. Transcriptomic signatures: Differentially expressed genes	113
3.5.2. Metabolic signatures: Reporter metabolites.....	117
3.5.3. Regulatory signatures: Reporter TFs and miRNAs.....	124
4. Conclusion.....	129
5. References	135

ABBREVIATIONS

- CAF:** Cancer-associated fibroblast
- CEPI:** Laser micro-dissected ovarian cancer epithelial cells
- CMC:** Differentially co-expressed module in OSE samples
- CMO:** Differentially co-expressed module in OSE samples
- CNC:** Co-expression network in CEPI samples
- CNO:** Co-expression network in OSE samples
- DEG:** Differentially Expressed Gene
- ECM:** Extracellular Matrix
- EOC:** Epithelial ovarian carcinoma
- GEO:** Gene Expression Omnibus
- HTRI:** Human Transcriptional Regulation Interactions database
- miRNA:** microRNA
- ncRNA:** non-coding RNA
- OSE:** Laser micro-dissected ovarian surface epithelia
- PCOS:** Polycystic ovarian syndrome
- PPI:** Protein-protein Interaction
- RT-PCR:** Real time polymerase chain reaction
- TCGA:** Cancer Genome Atlas
- TF:** Transcription Factor



5. REFERENCES

- Agarwal, S., Saini, S., Parashar, D., Verma, A., Sinha, A., Jagadish, N., Batra, A., Suri, S., Gupta, A., Ansari, A.S. (2013). The novel cancer-testis antigen A-kinase anchor protein 4 (AKAP4) is a potential target for immunotherapy of ovarian serous carcinoma. *Oncoimmunology* 2, e24270.
- Altomare, D.A., Testa, J.R. (2005). Perturbations of the AKT signaling pathway in human cancer. *Oncogene* 24, 7455-7464.
- Ambros, V. (2004). The functions of animal microRNAs. *Nature* 431, 350-355.
- Anam, M.T., Ishika, A., Hossain, M.B. (2015). A meta-analysis of hypoxia inducible factor 1-alpha (HIF1A) gene polymorphisms: association with cancers. *Biomarker research* 3, 29.
- Antony, P.M., Balling, R., Vlassis, N. (2012). From systems biology to systems biomedicine. *Current opinion in biotechnology* 23, 604-608.
- Aragon-Ching, J.B. (2014). The evolution of prostate cancer therapy: targeting the androgen receptor. *Frontiers in oncology* 4, 295.
- Arend, R.C., Londoño-Joshi, A.I., Samant, R.S., Li, Y., Conner, M., Hidalgo, B., Alvarez, R.D., Landen, C.N., Straughn, J.M., Buchsbaum, D.J. (2014). Inhibition of Wnt/β-catenin pathway by niclosamide: A therapeutic target for ovarian cancer. *Gynecologic oncology* 134, 112-120.
- Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T. (2000). Gene Ontology: tool for the unification of biology. *Nature genetics* 25, 25-29.
- Assenov, Y., Ramírez, F., Schelhorn, S.-E., Lengauer, T., Albrecht, M. (2008). Computing topological parameters of biological networks. *Bioinformatics* 24, 282-284.
- Atiomo, W., Daykin, C. (2012). Metabolomic biomarkers in women with polycystic ovary syndrome: a pilot study. *Molecular human reproduction* 18, 546-553.
- Aviel-Ronen, S., Soriano, D., Shmuel, E., Schonman, R., Rosenblatt, K., Zadok, O., Vituri, A., Seidman, D., Barshack, I., Cohen, Y. (2014). Surgically treated ovarian endometriosis association with BRCA1 and BRCA2 mutations. *Pathology-Research and Practice* 210, 250-255.
- Awwad, H.M., Geisel, J., Obeid, R. (2012). The role of choline in prostate cancer. *Clinical biochemistry* 45, 1548-1553.
- Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H.F., Futterweit, W., Janssen, O.E., Legro, R.S., Norman, R.J., Taylor, A.E. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility* 91, 456-488.
- Bader, G.D., Betel, D., Hogue, C.W. (2003). BIND: the biomolecular interaction network database. *Nucleic acids research* 31, 248-250.
- Bain, M.A., Faull, R., Fornasini, G., Milne, R.W., Evans, A.M. (2006). Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease.

- se patients undergoing haemodialysis. *Nephrology Dialysis Transplantation* 21, 1300-1304.
- Banerji, C.R., Miranda-Saavedra, D., Severini, S., Widschwendter, M., Enver, T., Zhou, J.X., Teschendorff, A.E. (2013). Cellular network entropy as the energy potential in Waddington's differentiation landscape. arXiv preprint arXiv:13107083.
- Barabasi, A.-L., Oltvai, Z.N. (2004). Network biology: understanding the cell's functional organization. *Nature reviews genetics* 5, 101-113.
- Barrett, T., Wilhite, S.E., Ledoux, P., Evangelista, C., Kim, I.F., Tomashevsky, M., Marshall, K.A., Phillippy, K.H., Sherman, P.M., Holko, M. (2013). NCBI GEO: archive for functional genomics data sets—update. *Nucleic acids research* 41, D991-D995.
- Bartel, D.P. (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *cell* 116, 281-297.
- Bauckman K, Campla C, Nanjundan M. (2012) Dysregulated TGFB signaling in ovarian cancer, *Ovarian Cancer - Basic Science Perspective*, Farghaly S. eds, ISBN: 978-953-307-812-0, InTech.
- Bauckman, K., Campla, C., Nanjundan, M. Dysregulated TGF β Signaling in Ovarian Cancer.
- Becker, K.G., Barnes, K.C., Bright, T.J., Wang, S.A. (2004). The genetic association database. *Nature genetics* 36, 431-432.
- Beckerman, R., Prives, C. (2010). Transcriptional regulation by p53. *Cold Spring Harbor perspectives in biology* 2, a000935.
- Bellelis, P., Podgaec, S., Brão, M.M. (2011). Environmental factors and endometriosis. *Revista da Associação Médica Brasileira (English Edition)* 57, 448-452.
- Bento, C., Andersson, M.K., Åman, P. (2009). DDIT3/CHOP and the sarcoma fusion oncoprotein FUS-DDIT3/TLS-CHOP bind cyclin-dependent kinase 2. *BMC cell biology* 10, 89.
- Bernatsky, S., Ramsey-Goldman, R., Labrecque, J., Joseph, L., Boivin, J.-F., Petri, M., Zoma, A., Manzi, S., Urowitz, M.B., Gladman, D. (2013). Cancer risk in systemic lupus: an updated international multi-centre cohort study. *Journal of autoimmunity* 42, 130-135.
- Bignotti, E., Tassi, R.A., Calza, S., Ravaggi, A., Romani, C., Rossi, E., Falchetti, M., Odicino, F.E., Pecorelli, S., Santin, A.D. (2006). Differential gene expression profiles between tumor biopsies and short-term primary cultures of ovarian serous carcinomas: identification of novel molecular biomarkers for early diagnosis and therapy. *Gynecologic oncology* 103, 405-416.
- Bignotti, E., Tassi, R.A., Calza, S., Ravaggi, A., Rossi, E., Donzelli, C., Todeschini, P., Romani, C., Bandiera, E., Zanotti, L. (2013). Secretoglobin expression in ovarian carcinoma: lipophilin B gene upregulation as an independent marker of better prognosis. *Journal of translational medicine* 11, 162.
- Blazejczyk, A., Switalska, M., Chlopicki, S., Marcinek, A., Gebicki, J., Nowak, M., Nasulewicz-Goldeman, A., Wietrzyk, J. (2016). 1-methylnicotinamide and its structural analog 1, 4-dimethylpyridine for the prevention of cancer metastasis. *Journal of Experimental & Clinical Cancer Research* 35, 110.

- Bodnar, L., Stanczak, A., Cierniak, S., Smoter, M., Cichowicz, M., Kozlowski, W., Szczylik, C., Wieczorek, M., Lamparska-Przybysz, M. (2014). Wnt/β-catenin pathway as a potential prognostic and predictive marker in patients with advanced ovarian cancer. *Journal of ovarian research* 7, 16.
- Bolstad, B.M., Irizarry, R.A., Åstrand, M., Speed, T.P. (2003). A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics* 19, 185-193.
- Books, A. (2012). Endometriosis-Basic Concepts and Current Research Trends.
- Bordbar, A., Feist, A.M., Usaite-Black, R., Woodcock, J., Palsson, B.O., Famili, I. (2011). A multi-tissue type genome-scale metabolic network for analysis of whole-body systems physiology. *BMC systems biology* 5, 180.
- Borhani, N., Manoochehri, M., Gargari, S.S., Novin, M.G., Mansouri, A., Omrani, M.D. (2014). Decreased expression of proapoptotic genes caspase-8-and BCL2-associated agonist of cell death (BAD) in ovarian cancer. *Clinical Ovarian and Other Gynecologic Cancer* 7, 18-23.
- Bovolenta, L.A., Acencio, M.L., Lemke, N. (2012). HTRIdb: an open-access database for experimentally verified human transcriptional regulation interactions. *BMC genomics* 13, 405.
- Bowen, N.J., Walker, L.D., Matyunina, L.V., Logani, S., Totten, K.A., Benigno, B.B., McDonald, J.F. (2009). Gene expression profiling supports the hypothesis that human ovarian surface epithelia are multipotent and capable of serving as ovarian cancer initiating cells. *BMC medical genomics* 2, 71.
- Brachova, P., Thiel, K.W., Leslie, K.K. (2013). The consequence of oncomorphic TP53 mutations in ovarian cancer. *International journal of molecular sciences* 14, 19257-19275.
- Budhu, A., Roessler, S., Zhao, X., Yu, Z., Forgues, M., Ji, J., Karoly, E., Qin, L.X., Ye, Q.H., Jia, H.L. (2013). Integrated metabolite and gene expression profiles identify lipid biomarkers associated with progression of hepatocellular carcinoma and patient outcomes. *Gastroenterology* 144, 1066-1075. e1061.
- Burotto, M., Chiou, V.L., Lee, J.M., Kohn, E.C. (2014). The MAPK pathway across different malignancies: a new perspective. *Cancer* 120, 3446-3456.
- Buyse, S.S., Partridge, E., Black, A., Johnson, C.C., Lamerato, L., Isaacs, C., Reding, D.J., Greenlee, R.T., Yokochi, L.A., Kessel, B. (2011). Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. *Jama* 305, 2295-2303.
- Buyse, T.P., Chari, R., Lee, E.H., Zhang, M., MacAulay, C., Lam, S., Lam, W.L., Ling, V. (2007). Genetic changes in the evolution of multidrug resistance for cultured human ovarian cancer cells. *Genes, Chromosomes and Cancer* 46, 1069-1079.
- Cai, S.-Y., Yang, T., Chen, Y., Wang, J.-W., Li, L., Xu, M.-J. (2015). Gene expression profiling of ovarian carcinomas and prognostic analysis of outcome. *Journal of ovarian research* 8, 50.
- Calimlioglu, B., Karagoz, K., Sevimoglu, T., Kilic, E., Gov, E., Arga, K.Y. (2015). Tissue-specific molecular biomarker signatures of type 2 diabetes: an integ-

- rative analysis of transcriptomics and protein–protein interaction data. *Omnis: a journal of integrative biology* 19, 563-573.
- Calin, G.A., Sevignani, C., Dumitru, C.D., Hyslop, T., Noch, E., Yendamuri, S., Shimizu, M., Rattan, S., Bullrich, F., Negrini, M. (2004). Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci U S A* 101, 2999-3004.
- Cannio, R.A., Moysich, K.B. (2015). Epithelial ovarian cancer and recreational physical activity: a review of the epidemiological literature and implications for exercise prescription. *Gynecologic oncology* 137, 559-573.
- Capaccione, K.M., Pine, S.R. (2013). The Notch signaling pathway as a mediator of tumor survival. *Carcinogenesis*, bgt127.
- Carbon, S., Ireland, A., Mungall, C.J., Shu, S., Marshall, B., Lewis, S., Group, W.P.W. (2009). AmiGO: online access to ontology and annotation data. *Bioinformatics* 25, 288-289.
- Cathcart, M.C., Gray, S.G., Baird, A.M., Boyle, E., Gately, K., Kay, E., Cummins, R., Pidgeon, G.P., O'byrne, K.J. (2011). Prostacyclin synthase expression and epigenetic regulation in nonsmall cell lung cancer. *Cancer* 117, 5121-5132.
- Chagoyen, M., Pazos, F. (2011). MBRole: enrichment analysis of metabolomic data. *Bioinformatics* 27, 730-731.
- Chakrabarty, A., Tranguch, S., Daikoku, T., Jensen, K., Furneaux, H., Dey, S.K. (2007). MicroRNA regulation of cyclooxygenase-2 during embryo implantation. *Proceedings of the National Academy of Sciences* 104, 15144-15149.
- Chandran, U.R., Ma, C., Dhir, R., Bisceglia, M., Lyons-Weiler, M., Liang, W., Michalopoulos, G., Becich, M., Monzon, F.A. (2007). Gene expression profiles of prostate cancer reveal involvement of multiple molecular pathways in the metastatic process. *BMC cancer* 7, 64.
- Chang, J.-H., Au, H.-K., Lee, W.-C., Chi, C.-C., Ling, T.-Y., Wang, L.-M., Kao, S.-H., Huang, Y.-H., Tzeng, C.-R. (2013). Expression of the pluripotent transcription factor OCT4 promotes cell migration in endometriosis. *Fertility and sterility* 99, 1332-1339. e1335.
- Chatr-Aryamontri, A., Breitkreutz, B.-J., Oughtred, R., Boucher, L., Heinicke, S., Chen, D., Stark, C., Breitkreutz, A., Kolas, N., O'donnell, L. (2015). The BioGRID interaction database: 2015 update. *Nucleic acids research* 43, D470-D478.
- Cheaiib, B., Auguste, A., Leary, A. (2015). The PI3K/Akt/mTOR pathway in ovarian cancer: therapeutic opportunities and challenges. *Chinese journal of cancer* 34, 4.
- Chen, C.-Y., Chen, S.-T., Fuh, C.-S., Juan, H.-F., Huang, H.-C. (2011). Coregulation of transcription factors and microRNAs in human transcriptional regulatory network. *BMC bioinformatics* 12, S41.
- Chen, F., Zhuang, X., Lin, L., Yu, P., Wang, Y., Shi, Y., Hu, G., Sun, Y. (2015). New horizons in tumor microenvironment biology: challenges and opportunities. *BMC medicine* 13, 45.
- Chen, L., Wang, S., Zhou, Y., Wu, X., Entin, I., Epstein, J., Yaccoby, S., Xiong, W., Barlogie, B., Shaughnessy, J.D. (2010). Identification of early growth respon-

- se protein 1 (EGR-1) as a novel target for JUN-induced apoptosis in multiple myeloma. *Blood* 115, 61-70.
- Chen, R., Alvero, A., Silasi, D., Kelly, M., Fest, S., Visintin, I., Leiser, A., Schwartz, P., Rutherford, T., Mor, G. (2008). Regulation of IKK β by miR-199a affects NF- κ B activity in ovarian cancer cells. *Oncogene* 27, 4712-4723.
- Chen, Y.-F., Chen, Y.-T., Chiu, W.-T., Shen, M.-R. (2013). Remodeling of calcium signaling in tumor progression. *Journal of biomedical science* 20, 23.
- Cheng, J.-C., Klausen, C., Leung, P.C. (2013a). Hypoxia-inducible factor 1 alpha mediates epidermal growth factor-induced down-regulation of E-cadherin expression and cell invasion in human ovarian cancer cells. *Cancer letters* 329, 197-206.
- Cheng, J., Chang, H., Leung, P. (2013b). Egr-1 mediates epidermal growth factor-induced downregulation of E-cadherin expression via Slug in human ovarian cancer cells. *Oncogene* 32, 1041-1049.
- Chiarugi, A., Dölle, C., Felici, R., Ziegler, M. (2012). The NAD metabolome—a key determinant of cancer cell biology. *Nature Reviews Cancer* 12, 741-752.
- Chin, C.-H., Chen, S.-H., Wu, H.-H., Ho, C.-W., Ko, M.-T., Lin, C.-Y. (2014). cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC systems biology* 8, S11.
- Chittenden, B., Fullerton, G., Maheshwari, A., Bhattacharya, S. (2009). Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. *Reproductive biomedicine online* 19, 398-405.
- Choi, C., Choi, J., Park, Y., Lee, Y., Song, S., Sung, C., Song, T., Kim, M., Kim, T., Lee, J. (2012). Identification of differentially expressed genes according to chemosensitivity in advanced ovarian serous adenocarcinomas: expression of GRIA2 predicts better survival. *British journal of cancer* 107, 91-99.
- Chou, C.-H., Chang, N.-W., Shrestha, S., Hsu, S.-D., Lin, Y.-L., Lee, W.-H., Yang, C.-D., Hong, H.-C., Wei, T.-Y., Tu, S.-J. (2016). miRTarBase 2016: updates to the experimentally validated miRNA-target interactions database. *Nucleic acids research* 44, D239-D247.
- Chou, J., Werb, Z. (2012). MicroRNAs play a big role in regulating ovarian cancer-associated fibroblasts and the tumor microenvironment. *Cancer discovery* 2, 1078-1080.
- Christian, S.L., Zu, D., Licursi, M., Komatsu, Y., Pongnopparat, T., Codner, D.A., Hirasawa, K. (2012). Suppression of IFN-induced transcription underlies IFN defects generated by activated Ras/MEK in human cancer cells. *PLoS One* 7, e44267.
- Clevers, H., Nusse, R. (2012). Wnt/ β -catenin signaling and disease. *Cell* 149, 1192-1205.
- Corney, D.C., Hwang, C.-I., Matoso, A., Vogt, M., Flesken-Nikitin, A., Godwin, A.K., Kamat, A.A., Sood, A.K., Ellenson, L.H., Hermeking, H. (2010). Frequent downregulation of miR-34 family in human ovarian cancers. *Clinical Cancer Research* 16, 1119-1128.
- Creighton, C.J., Hernandez-Herrera, A., Jacobsen, A., Levine, D.A., Mankoo, P., Schultz, N., Du, Y., Zhang, Y., Larsson, E., Sheridan, R. (2012). Integrated

- analyses of microRNAs demonstrate their widespread influence on gene expression in high-grade serous ovarian carcinoma. PLoS One 7, e34546.
- Croce, C.M. (2009). Causes and consequences of microRNA dysregulation in cancer. *Nature reviews genetics* 10, 704-714.
- Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., Caudy, M., Garapati, P., Gopinath, G., Jassal, B. (2010). Reactome: a database of reactions, pathways and biological processes. *Nucleic acids research*, gkq1018.
- Cui, J., Zhu, L., Xia, X., Wang, H.Y., Legras, X., Hong, J., Ji, J., Shen, P., Zheng, S., Chen, Z.J. (2010). NLRC5 negatively regulates the NF- κ B and type I interferon signaling pathways. *Cell* 141, 483-496.
- Cybulski, M., Jeleniewicz, W., Nowakowski, A., Stenzel-Bembenek, A., Tarkowski, R., Kotarski, J., Stepulak, A. (2015). Cyclin I mRNA Expression Correlates with Kinase Insert Domain Receptor Expression in Human Epithelial Ovarian Cancer. *Anticancer research* 35, 1115-1119.
- Dandara, C., Endrenyi, L., Kolker, E., Hekim, N., Steuten, L.M., Güngör, K., Akilli, E., Özdemir, V. (2016). Precision Medicine 2.0: The Rise of Glocal Innovation, Superconnectors, and Design Thinking (Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA).
- Davidson, B., Holth, A., Hellesylt, E., Hadar, R., Katz, B., Tropé, C.G., Reich, R. (2016). HUR mRNA expression in ovarian high-grade serous carcinoma effusions is associated with poor survival. *Human pathology* 48, 95-101.
- de la Fuente, A. (2010). From 'differential expression' to 'differential networking'—identification of dysfunctional regulatory networks in diseases. *Trends in genetics* 26, 326-333.
- Deng, J., Wang, L., Chen, H., Li, L., Ma, Y., Ni, J., Li, Y. (2013). The role of tumour-associated MUC1 in epithelial ovarian cancer metastasis and progression. *Cancer and Metastasis Reviews* 32, 535-551.
- Desai, V., Prasad, N.R., Manohar, S.M., Sachan, A., Narasimha, S.R.P.V.L., Bitla, A.R.R. (2014). Oxidative stress in non-obese women with polycystic ovarian syndrome. *Journal of clinical and diagnostic research: JCDR* 8, CC01.
- Dews, M., Homayouni, A., Yu, D., Murphy, D., Sevignani, C., Wentzel, E., Furth, E.E., Lee, W.M., Enders, G.H., Mendell, J.T. (2006). Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. *Nature genetics* 38, 1060-1065.
- Dezső, Z., Oestreicher, J., Weaver, A., Santiago, S., Agoulnik, S., Chow, J., Oda, Y., Funahashi, Y. (2014). Gene expression profiling reveals epithelial mesenchymal transition (EMT) genes can selectively differentiate eribulin sensitive breast cancer cells. *PLoS One* 9, e106131.
- Didžiapatrienė, J., Bublevič, J., Smailytė, G., Kazbarienė, B., Stukas, R. (2014). Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients. *Medicina* 50, 204-208.
- Dittmer, J. (2003). The biology of the Ets1 proto-oncogene. *Molecular cancer* 2, 29.

- Dobbin, Z.C., Landen, C.N. (2013). The importance of the PI3K/AKT/MTOR pathway in the progression of ovarian cancer. International journal of molecular sciences 14, 8213-8227.
- Doig, T.N., Hume, D.A., Theocharidis, T., Goodlad, J.R., Gregory, C.D., Freeman, T.C. (2013). Coexpression analysis of large cancer datasets provides insight into the cellular phenotypes of the tumour microenvironment. BMC genomics 14, 469.
- Dong, Y., Li, J., Han, F., Chen, H., Zhao, X., Qin, Q., Shi, R., Liu, J. (2015). High IGF2 expression is associated with poor clinical outcome in human ovarian cancer. Oncology reports 34, 936-942.
- Duarte, N.C., Becker, S.A., Jamshidi, N., Thiele, I., Mo, M.L., Vo, T.D., Srivas, R., Palsson, B.Ø. (2007). Global reconstruction of the human metabolic network based on genomic and bibliomic data. Proceedings of the National Academy of Sciences 104, 1777-1782.
- Ducros, E., Mirshahi, S., Azzazene, D., Camilleri-Broët, S., Mery, E., Al Farsi, H., Althawadi, H., Besbess, S., Chidiac, J., Pujade-Lauraine, E. (2012). Endothelial protein C receptor expressed by ovarian cancer cells as a possible biomarker of cancer onset. International journal of oncology 41, 433-440.
- Duesberg, P., Li, R., Fabarius, A., Hehlmann, R. (2006). Aneuploidy and cancer: from correlation to causation. In Infection and inflammation: impacts on oncogenesis (Karger Publishers), pp. 16-44.
- Dutta, P., Bui, T., Bauckman, K.A., Keyomarsi, K., Mills, G.B., Nanjundan, M. (2013). EVI1 splice variants modulate functional responses in ovarian cancer cells. Molecular oncology 7, 647-668.
- Dwivedi, S.K.D., Mustafi, S.B., Mangala, L.S., Jiang, D., Pradeep, S., Rodriguez-Aguayo, C., Ling, H., Ivan, C., Mukherjee, P., Calin, G.A. (2016). Therapeutic evaluation of microRNA-15a and microRNA-16 in ovarian cancer. Oncotarget 7, 15093.
- Erhard, F., Haas, J., Lieber, D., Malterer, G., Jaskiewicz, L., Zavolan, M., Dölken, L., Zimmer, R. (2014). Widespread context dependency of microRNA-mediated regulation. Genome research 24, 906-919.
- Erickson, B.K., Conner, M.G., Landen, C.N. (2013). The role of the fallopian tube in the origin of ovarian cancer. American journal of obstetrics and gynecology 209, 409-414.
- Fagerberg, L., Hallström, B.M., Oksvold, P., Kampf, C., Djureinovic, D., Odeberg, J., Habuka, M., Tahmasebpoor, S., Danielsson, A., Edlund, K. (2014). Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Molecular & Cellular Proteomics 13, 397-406.
- Farooqi, A.A., Qureshi, M.Z., Coskunpinar, E., Naqvi, S., Yaylim, I., Ismail, M. (2014). MiR-421, miR-155 and miR-650: emerging trends of regulation of cancer and apoptosis. Asian Pac J Cancer Prev 15, 1909-1912.
- Fekete, T., Rásó, E., Pete, I., Tegze, B., Liko, I., Munkácsy, G., Sipos, N., Rigó, J., Györfi, B. (2012). Meta-analysis of gene expression profiles associated with

- histological classification and survival in 829 ovarian cancer samples. International journal of cancer 131, 95-105.
- Filigheddu, N., Gregnanin, I., Porporato, P.E., Surico, D., Perego, B., Galli, L., Patrignani, C., Graziani, A., Surico, N. (2010). Differential expression of microRNAs between eutopic and ectopic endometrium in ovarian endometriosis. BioMed Research International 2010.
- Filipowicz, W., Jaskiewicz, L., Kolb, F.A., Pillai, R.S. (2005). Post-transcriptional gene silencing by siRNAs and miRNAs. Current opinion in structural biology 15, 331-341.
- Fishilevich, S., Zimmerman, S., Kohn, A., Stein, T.I., Olander, T., Kolker, E., Safar, M., Lancet, D. (2016). Genic insights from integrated human proteomics in GeneCards. Database 2016, baw030.
- Flesken-Nikitin, A., Hwang, C.-I., Cheng, C.-Y., Michurina, T.V., Enikolopov, G., Nikitin, A.Y. (2013). Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche. Nature 495, 241-245.
- Fong, M.Y., McDunn, J., Kakar, S.S. (2011). Identification of metabolites in the normal ovary and their transformation in primary and metastatic ovarian cancer. PLoS One 6, e19963.
- Frampton, A.E., Castellano, L., Colombo, T., Giovannetti, E., Krell, J., Jacob, J., Pellegrino, L., Roca-Alonso, L., Funel, N., Gall, T.M. (2014). MicroRNAs co-operatively inhibit a network of tumor suppressor genes to promote pancreatic tumor growth and progression. Gastroenterology 146, 268-277. e218.
- Gajewski, T.F., Schreiber, H., Fu, Y.-X. (2013). Innate and adaptive immune cells in the tumor microenvironment. Nature immunology 14, 1014-1022.
- Gambardella, G., Moretti, M.N., De Cegli, R., Cardone, L., Peron, A., Di Bernardo, D. (2013). Differential network analysis for the identification of condition-specific pathway activity and regulation. Bioinformatics 29, 1776-1785.
- Garcia-Albornoz, M., Thankaswamy-Kosalai, S., Nilsson, A., Väremo, L., Nookaew, I., Nielsen, J. (2014). BioMet Toolbox 2.0: genome-wide analysis of metabolism and omics data. Nucleic acids research, gku371.
- Garg, M., Chaurasia, D., Rana, R., Jagadish, N., Kanodia, D., Dudha, N., Kamran, N., Salhan, S., Bhatnagar, A., Suri, S. (2007). Sperm-associated antigen 9, a novel cancer testis antigen, is a potential target for immunotherapy in epithelial ovarian cancer. Clinical Cancer Research 13, 1421-1428.
- Gatcliffe, T., Monk, B., Planutis, K., Holcombe, R. (2008). Wnt signaling in ovarian tumorigenesis. International Journal of Gynecological Cancer 18, 954-962.
- Gatt, S., Dagan, A. (2012). Cancer and sphingolipid storage disease therapy using novel synthetic analogs of sphingolipids. Chemistry and physics of lipids 165, 462-474.
- Gautier, L., Cope, L., Bolstad, B.M., Irizarry, R.A. (2004). affy—analysis of Affymetrix GeneChip data at the probe level. Bioinformatics 20, 307-315.
- Gennarino, V.A., D'Angelo, G., Dharmalingam, G., Fernandez, S., Russolillo, G., Sanges, R., Mutarelli, M., Belcastro, V., Ballabio, A., Verde, P. (2012). Identification of microRNA-regulated gene networks by expression analysis of target genes. Genome research 22, 1163-1172.

- Gentleman, R.C., Carey, V.J., Bates, D.M., Bolstad, B., Dettling, M., Dudoit, S., Ellis, B., Gautier, L., Ge, Y., Gentry, J. (2004). Bioconductor: open software development for computational biology and bioinformatics. *Genome biology* 5, R80.
- Gibellini, F., Smith, T.K. (2010). The Kennedy pathway—de novo synthesis of phosphatidylethanolamine and phosphatidylcholine. *IUBMB life* 62, 414-428.
- Gill, R., Datta, S., Datta, S. (2014). Differential network analysis in human cancer research. *Current pharmaceutical design* 20, 4-10.
- Glass, K., Quackenbush, J., Spentzos, D., Haibe-Kains, B., Yuan, G.-C. (2015). A network model for angiogenesis in ovarian cancer. *BMC bioinformatics* 16, 115.
- Gloss, B.S., Patterson, K.I., Barton, C.A., Gonzalez, M., Scurry, J.P., Hacker, N.F., Sutherland, R.L., O'Brien, P.M., Clark, S.J. (2012). Integrative genome-wide expression and promoter DNA methylation profiling identifies a potential novel panel of ovarian cancer epigenetic biomarkers. *Cancer letters* 318, 76-85.
- Gov, E., Arga, K.Y. (2014). Genetic mutations are characterized by increase in entropy at the transcriptional level. *Journal of Biological Systems* 22, 377-391.
- Gov, E., Arga, K.Y. (2016). Interactive cooperation and hierarchical operation of microRNA and transcription factor crosstalk in human transcriptional regulatory network. *IET Systems Biology* 10, 219-228.
- Govatati, S., Challa, K., Reddy, S.B., Pramod, K., Deenadayal, M., Chakravarty, B., Shivaji, S., Bhanoori, M. (2015). BRCA1 alterations are associated with endometriosis, but BRCA2 alterations show no detectable endometriosis risk: a study in Indian population. *Journal of assisted reproduction and genetics* 32, 277-285.
- Goyama, S., Schibler, J., Cunningham, L., Zhang, Y., Rao, Y., Nishimoto, N., Nakagawa, M., Olsson, A., Wunderlich, M., Link, K.A. (2013). Transcription factor RUNX1 promotes survival of acute myeloid leukemia cells. *The Journal of clinical investigation* 123, 3876-3888.
- Grammatikakis, I., Gorospe, M., Abdelmohsen, K. (2013). Modulation of cancer traits by tumor suppressor microRNAs. *International journal of molecular sciences* 14, 1822-1842.
- Grochow, J.A., Kellis, M. (2007). Network motif discovery using subgraph enumeration and symmetry-breaking. Paper presented at: Annual International Conference on Research in Computational Molecular Biology (Springer).
- Groeneweg, J.W., DiGloria, C.M., Yuan, J., Richardson, W.S., Growdon, W.B., Sathyaranarayanan, S., Foster, R., Rueda, B.R. (2014a). Inhibition of notch signaling in combination with Paclitaxel reduces platinum-resistant ovarian tumor growth. *Frontiers in oncology* 4, 171.
- Groeneweg, J.W., Foster, R., Growdon, W.B., Verheijen, R.H., Rueda, B.R. (2014b). Notch signaling in serous ovarian cancer. *Journal of ovarian research* 7, 95.
- Grosswendt, S., Filipchyk, A., Manzano, M., Klironomos, F., Schilling, M., Herzog, M., Gottwein, E., Rajewsky, N. (2014). Unambiguous identification of

- miRNA: target site interactions by different types of ligation reactions. Molecular cell 54, 1042-1054.
- Gruosso, T., Garnier, C., Abelanet, S., Kieffer, Y., Lemesre, V., Bellanger, D., Bieche, I., Marangoni, E., Sastre-Garau, X., Mieulet, V. (2015). MAP3K8/TPL-2/COT is a potential predictive marker for MEK inhibitor treatment in high-grade serous ovarian carcinomas. Nature communications 6.
- Guo, A.-Y., Sun, J., Jia, P., Zhao, Z. (2010). A novel microRNA and transcription factor mediated regulatory network in schizophrenia. BMC systems biology 4, 10.
- Guo, L.M., Pu, Y., Han, Z., Liu, T., Li, Y.X., Liu, M., Li, X., Tang, H. (2009). MicroRNA-9 inhibits ovarian cancer cell growth through regulation of NF- κ B1. FEBS journal 276, 5537-5546.
- Gutman, G., Barak, V., Maslovitz, S., Amit, A., Lessing, J.B., Geva, E. (2008). Regulation of vascular endothelial growth factor-A and its soluble receptor sFlt-1 by luteinizing hormone in vivo: implication for ovarian follicle angiogenesis. Fertility and sterility 89, 922-926.
- Han, M., Liu, M., Wang, Y., Chen, X., Xu, J., Sun, Y., Zhao, L., Qu, H., Fan, Y., Wu, C. (2012). Antagonism of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell phenotype through AKT/ERK1/2 inactivation by targeting PTEN. PLoS One 7, e39520.
- Hanahan, D., Coussens, L.M. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer cell 21, 309-322.
- Harris, H.R., Cramer, D.W., Vitonis, A.F., DePari, M., Terry, K.L. (2012). Folate, vitamin B6, vitamin B12, methionine and alcohol intake in relation to ovarian cancer risk. International journal of cancer 131, E518-E529.
- Harris, S.L., Levine, A.J. (2005). The p53 pathway: positive and negative feedback loops. Oncogene 24, 2899-2908.
- Hata, K., Dhar, D.K., Watanabe, Y., Nakai, H., Hoshiai, H. (2007). Expression of metastin and a G-protein-coupled receptor (AXOR12) in epithelial ovarian cancer. European Journal of Cancer 43, 1452-1459.
- Hatakeyama, S. (2011). TRIM proteins and cancer. Nature Reviews Cancer 11, 792-804.
- Hayat, M. (2016). Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging: Volume 9: Human Diseases and Autophagosome (Academic Press).
- Hayes, J., Peruzzi, P.P., Lawler, S. (2014). MicroRNAs in cancer: biomarkers, functions and therapy. Trends in molecular medicine 20, 460-469.
- He, H., Jazdzewski, K., Li, W., Liyanarachchi, S., Nagy, R., Volinia, S., Calin, G.A., Liu, C.-g., Franssila, K., Suster, S. (2005). The role of microRNA genes in papillary thyroid carcinoma. Proc Natl Acad Sci U S A 102, 19075-19080.
- He, J., Jing, Y., Li, W., Qian, X., Xu, Q., Li, F.-S., Liu, L.-Z., Jiang, B.-H., Jiang, Y. (2013). Roles and mechanism of miR-199a and miR-125b in tumor angiogenesis. PLoS One 8, e56647.

- He, L., He, X., Lim, L.P., De Stanchina, E., Xuan, Z., Liang, Y., Xue, W., Zender, L., Magnus, J., Ridzon, D. (2007). A microRNA component of the p53 tumour suppressor network. *Nature* 447, 1130-1134.
- Heo, J.H., Song, J.-y., Jeong, J.-y., Kim, G., Kim, T.H., Kang, H., Kwon, A.-y., An, H.J. (2016). Fibulin-5 is a tumour suppressor inhibiting cell migration and invasion in ovarian cancer. *Journal of clinical pathology* 69, 109-116.
- Hever, A., Roth, R.B., Hevezzi, P., Marin, M.E., Acosta, J.A., Acosta, H., Rojas, J., Herrera, R., Grigoriadis, D., White, E. (2007). Human endometriosis is associated with plasma cells and overexpression of B lymphocyte stimulator. *Proceedings of the National Academy of Sciences* 104, 12451-12456.
- Hippisley-Cox, J., Coupland, C. (2012). Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm. *Bmj* 344, d8009.
- Hira, S., Tomita, T., Matsui, T., Igarashi, K., Ikeda-Saito, M. (2007). Bach1, a heme-dependent transcription factor, reveals presence of multiple heme binding sites with distinct coordination structure. *IUBMB life* 59, 542-551.
- Robert, O. (2008). Gene regulation by transcription factors and microRNAs. *Science* 319, 1785-1786.
- Hornstein, E., Shomron, N. (2006). Canalization of development by microRNAs. *Nature genetics* 38, S20-S24.
- Hsiao, T.-H., Chiu, Y.-C., Hsu, P.-Y., Lu, T.-P., Lai, L.-C., Tsai, M.-H., Huang, T.H.-M., Chuang, E.Y., Chen, Y. (2016). Differential network analysis reveals the genome-wide landscape of estrogen receptor modulation in hormonal cancers. *Scientific reports* 6.
- Hsu, C.-L., Juan, H.-F., Huang, H.-C. (2015). Functional analysis and characterization of differential coexpression networks. *Scientific reports* 5, 13295.
- Huang, D.W., Sherman, B.T., Lempicki, R.A. (2009). Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. *Nucleic acids research* 37, 1-13.
- Huang, Y., Shen, X.J., Zou, Q., Wang, S.P., Tang, S.M., Zhang, G.Z. (2011). Biological functions of microRNAs: a review. *Journal of physiology and biochemistry* 67, 129-139.
- Huang, Y.-W., Chen, C., Xu, M.-M., Li, J.-D., Xiao, J., Zhu, X.-F. (2013). Expression of c-Src and phospho-Src in epithelial ovarian carcinoma. *Molecular and cellular biochemistry* 376, 73-79.
- Huff, L.P., DeCristo, M.J., Trembath, D., Kuan, P.F., Yim, M., Liu, J., Cook, D.R., Miller, C.R., Der, C.J., Cox, A.D. (2013). The role of Ect2 nuclear RhoGEF activity in ovarian cancer cell transformation. *Genes & cancer* 4, 460-475.
- Ideker, T., Krogan, N.J. (2012). Differential network biology. *Molecular systems biology* 8, 565.
- Iorio, E., Ricci, A., Bagnoli, M., Pisanu, M.E., Castellano, G., Di Vito, M., Venturini, E., Glunde, K., Bhujwalla, Z.M., Mezzanzanica, D. (2010). Activation of phosphatidylcholine cycle enzymes in human epithelial ovarian cancer cells. *Cancer research* 70, 2126-2135.

- Iorio, M.V., Croce, C.M. (2012). MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. *EMBO molecular medicine* 4, 143-159.
- Iorio, M.V., Visone, R., Di Leva, G., Donati, V., Petrocca, F., Casalini, P., Taccioli, C., Volinia, S., Liu, C.-G., Alder, H. (2007). MicroRNA signatures in human ovarian cancer. *Cancer research* 67, 8699-8707.
- Iozzo, R.V., Sanderson, R.D. (2011). Proteoglycans in cancer biology, tumour microenvironment and angiogenesis. *Journal of cellular and molecular medicine* 15, 1013-1031.
- Iwanaga, R., Komori, H., Ishida, S., Okamura, N., Nakayama, K., Nakayama, K., Ohtani, K. (2006). Identification of novel E2F1 target genes regulated in cell cycle-dependent and independent manners. *Oncogene* 25, 1786-1798.
- Jensen, L.E., Whitehead, A.S. (2003). Ubiquitin activated tumor necrosis factor receptor associated factor-6 (TRAF6) is recycled via deubiquitination. *FEBS letters* 553, 190-194.
- Jiang, L., Huang, J., Li, L., Chen, Y., Chen, X., Zhao, X., Yang, D. (2015). MicroRNA-93 promotes ovarian granulosa cells proliferation through targeting CDKN1A in polycystic ovarian syndrome. *The Journal of Clinical Endocrinology & Metabolism* 100, E729-E738.
- Jiang, Q., Wang, Y., Hao, Y., Juan, L., Teng, M., Zhang, X., Li, M., Wang, G., Liu, Y. (2009). miR2Disease: a manually curated database for microRNA deregulation in human disease. *Nucleic acids research* 37, D98-D104.
- Jin, K.L., Pak, J.H., Park, J.-Y., Choi, W.H., Lee, J.-Y., Kim, J.-H., Nam, J.-H. (2008). Expression profile of histone deacetylases 1, 2 and 3 in ovarian cancer tissues. *Journal of gynecologic oncology* 19, 185-190.
- Jin, N., Wu, H., Miao, Z., Huang, Y., Hu, Y., Bi, X., Wu, D., Qian, K., Wang, L., Wang, C. (2015). Network-based survival-associated module biomarker and its crosstalk with cell death genes in ovarian cancer. *Scientific reports* 5.
- Johansson, J., Stener-Victorin, E. (2013). Polycystic ovary syndrome: effect and mechanisms of acupuncture for ovulation induction. *Evidence-Based Complementary and Alternative Medicine* 2013.
- Joshi, H.P., Subramanian, I.V., Schnettler, E.K., Ghosh, G., Rupaimoole, R., Evans, C., Saluja, M., Jing, Y., Cristina, I., Roy, S. (2014). Dynamin 2 along with microRNA-199a reciprocally regulate hypoxia-inducible factors and ovarian cancer metastasis. *Proceedings of the National Academy of Sciences* 111, 5331-5336.
- Ju, W., Yoo, B.C., Kim, I.-J., Kim, J.W., Kim, S.C., Lee, H.P. (2009). Identification of genes with differential expression in chemoresistant epithelial ovarian cancer using high-density oligonucleotide microarrays. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics* 18, 47-56.
- Kamburov, A., Grossmann, A., Herwig, R., Stelzl, U. (2012). Cluster-based assessment of protein-protein interaction confidence. *BMC bioinformatics* 13, 262.
- Kan, C.W., Hahn, M.A., Gard, G.B., Maidens, J., Huh, J.Y., Marsh, D.J., Howell, V.M. (2012). Elevated levels of circulating microRNA-200 family members correlate with serous epithelial ovarian cancer. *BMC cancer* 12, 627.

- Kanehisa, M., Goto, S., Sato, Y., Kawashima, M., Furumichi, M., Tanabe, M. (2014). Data, information, knowledge and principle: back to metabolism in KEGG. *Nucleic acids research* 42, D199-D205.
- Karagoz, K., L Lehman, H., B Stairs, D., Sinha, R., Y Arga, K. (2016a). Proteomic and metabolic signatures of esophageal squamous cell carcinoma. *Current cancer drug targets* 16, 721-736.
- Karagoz, K., Sevimoglu, T., Arga, K.Y. (2016b). Integration of multiple biological features yields high confidence human protein interactome. *Journal of theoretical biology* 403, 85-96.
- Karagoz, K., Sinha, R., Arga, K.Y. (2015). Triple negative breast cancer: a multi-omics network discovery strategy for candidate targets and driving pathways. *Omics: a journal of integrative biology* 19, 115-130.
- Kau, T.R., Way, J.C., Silver, P.A. (2004). Nuclear transport and cancer: from mechanism to intervention. *Nature Reviews Cancer* 4, 106-117.
- Ke, C., Hou, Y., Zhang, H., Fan, L., Ge, T., Guo, B., Zhang, F., Yang, K., Wang, J., Lou, G. (2015). Large-scale profiling of metabolic dysregulation in ovarian cancer. *International journal of cancer* 136, 516-526.
- Kenigsberg, S., Bentov, Y., Chalifa-Caspi, V., Potashnik, G., Ofir, R., Birk, O.S. (2009). Gene expression microarray profiles of cumulus cells in lean and overweight-obese polycystic ovary syndrome patients. *Molecular human reproduction*.
- Khamas, A., Ishikawa, T., Shimokawa, K., Mogushi, K., Iida, S., Ishiguro, M., Mizushima, H., Tanaka, H., Uetake, H., Sugihara, K. (2012). Screening for epigenetically masked genes in colorectal cancer Using 5-Aza-2'-deoxycytidine, microarray and gene expression profile. *Cancer Genomics-Proteomics* 9, 67-75.
- Kim, J.-E., Billadeau, D.D., Chen, J. (2005). The tandem BRCT domains of Ect2 are required for both negative and positive regulation of Ect2 in cytokinesis. *Journal of Biological Chemistry* 280, 5733-5739.
- King, E.R., Tung, C.S., Tsang, Y.T., Zu, Z., Lok, G.T., Deavers, M.T., Malpica, A., Wolf, J.K., Lu, K.H., Birrer, M.J. (2011). The anterior gradient homolog 3 (AGR3) gene is associated with differentiation and survival in ovarian cancer. *The American journal of surgical pathology* 35, 904.
- Klemm, F., Joyce, J.A. (2015). Microenvironmental regulation of therapeutic response in cancer. *Trends in cell biology* 25, 198-213.
- Ko, S.Y., Barengo, N., Ladanyi, A., Lee, J.-S., Marini, F., Lengyel, E., Naora, H. (2012). HOXA9 promotes ovarian cancer growth by stimulating cancer-associated fibroblasts. *The Journal of clinical investigation* 122, 3603-3617.
- Komatsu, K., Nakanishi, Y., Nemoto, N., Hori, T., Sawada, T., Kobayashi, M. (2004). Expression and quantitative analysis of matrix metalloproteinase-2 and -9 in human gliomas. *Brain tumor pathology* 21, 105-112.
- Komiyama, S., Kurahashi, T., Ishikawa, M., Tanaka, K., Komiyama, M., Mikami, M., Udagawa, Y. (2011). Expression of TGF β 1 and its receptors is associated with biological features of ovarian cancer and sensitivity to paclitaxel/carboplatin. *Oncology reports* 25, 1131.

- Kori, M., Gov, E., Arga, K.Y. (2016). Molecular signatures of ovarian diseases: Insights from network medicine perspective. *Systems Biology in Reproductive Medicine* 62, 266-282.
- Korpal, M., Lee, E.S., Hu, G., Kang, Y. (2008). The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. *Journal of Biological Chemistry* 283, 14910-14914.
- Koti, M., Gooding, R.J., Nuin, P., Haslehurst, A., Crane, C., Weerpals, J., Childds, T., Bryson, P., Dharsee, M., Evans, K. (2013). Identification of the IGF1/PI3K/NF κB/ERK gene signalling networks associated with chemotherapy resistance and treatment response in high-grade serous epithelial ovarian cancer. *BMC cancer* 13, 549.
- Kubiczkova, L., Sedlarikova, L., Hajek, R., Sevcikova, S. (2012). TGF- β -an excellent servant but a bad master. *Journal of translational medicine* 10, 183.
- Kulbe, H., Chakravarty, P., Leinster, D.A., Charles, K.A., Kwong, J., Thompson, R.G., Coward, J.I., Schioppa, T., Robinson, S.C., Gallagher, W.M. (2012). A dynamic inflammatory cytokine network in the human ovarian cancer microenvironment. *Cancer research* 72, 66-75.
- Lachej, N., Didžiapetrienė, J., Kazbarienė, B., Kanopienė, D., Jonušienė, V. (2013). Association between Notch signaling pathway and cancer. *Acta medica Lituanica* 19.
- Lamarre, S.G., Morrow, G., Macmillan, L., Brosnan, M.E., Brosnan, J.T. (2013). Formate: an essential metabolite, a biomarker, or more? *Clinical chemistry and laboratory medicine* 51, 571-578.
- Lau, T., Chan, L.K., Wong, E.C., Hui, C.W., Sneddon, K., Cheung, T., Yim, S., Lee, J.H., Yeung, C.S., Chung, T.K. (2017). A loop of cancer-stroma-cancer interaction promotes peritoneal metastasis of ovarian cancer via TNF α -TGF α -EGFR. *Oncogene*.
- Laudanski, P., Charkiewicz, R., Kuznicki, M., Szamatowicz, J., Charkiewicz, A., Niklinski, J. (2013). MicroRNAs expression profiling of eutopic proliferative endometrium in women with ovarian endometriosis. *Reproductive Biology and Endocrinology* 11, 78.
- Lawrenson, K., Grun, B., Lee, N., Mhawech-Fauceglia, P., Kan, J., Swenson, S., Lin, Y.G., Pejovic, T., Millstein, J., Gayther, S.A. (2015). NPPB is a novel candidate biomarker expressed by cancer-associated fibroblasts in epithelial ovarian cancer. *International journal of cancer* 136, 1390-1401.
- Le Page, C., Ouellet, V., Quinn, M.C., Tonin, P.N., Provencher, D.M., Mes-Masson, A.-M. (2008). BTF4/BTNA3. 2 and GCS as candidate mRNA prognostic markers in epithelial ovarian cancer. *Cancer Epidemiology and Prevention Biomarkers* 17, 913-920.
- Le, T.D., Liu, L., Liu, B., Tsykin, A., Goodall, G.J., Satou, K., Li, J. (2013). Inferring microRNA and transcription factor regulatory networks in heterogeneous data. *BMC bioinformatics* 14, 92.
- Leary, A., Auclin, E., Pautier, P., Lhommé, C. (2013). The PI3K/Akt/mTOR pathway in ovarian cancer: biological rationale and therapeutic opportunities. *Ovarian cancer-a clinical and translational update Croatia: InTech*, 275-302.

- Lecca, P., Re, A. (2015). Detecting modules in biological networks by edge weight clustering and entropy significance. *Frontiers in genetics* 6, 265.
- Lei, Y.-Y., Wang, W.-J., Mei, J.-H., Wang, C.-L. (2014). Mitogen-activated protein in kinase signal transduction in solid tumors. *Asian Pac J Cancer Prev* 15, 8539-8548.
- Lewis, B.P., Shih, I.-h., Jones-Rhoades, M.W., Bartel, D.P., Burge, C.B. (2003). Prediction of mammalian microRNA targets. *Cell* 115, 787-798.
- Li, B.-Q., Huang, T., Liu, L., Cai, Y.-D., Chou, K.-C. (2012). Identification of colorectal cancer related genes with mRMR and shortest path in protein-protein interaction network. *PLoS One* 7, e33393.
- Li, F., Wang, H., Feng, X., Li, P., Shu, T., Zhao, X., Li, B. (2016). Expression and clinical significance of ELOVL6 gene in high-grade serous ovarian carcinoma. *Zhonghua fu chan ke za zhi* 51, 192-197.
- Li, H., Xie, S., Liu, M., Chen, Z., Liu, X., Wang, L., Li, D., Zhou, Y. (2014a). The clinical significance of downregulation of mir-124-3p, mir-146a-5p, mir-155-5p and mir-335-5p in gastric cancer tumorigenesis. *International journal of oncology* 45, 197-208.
- Li, H., Zeng, J., Shen, K. (2014b). PI3K/AKT/mTOR signaling pathway as a therapeutic target for ovarian cancer. *Archives of gynecology and obstetrics* 290, 1067-1078.
- Li, M., Balch, C., Montgomery, J.S., Jeong, M., Chung, J.H., Yan, P., Huang, T.H., Kim, S., Nephew, K.P. (2009). Integrated analysis of DNA methylation and gene expression reveals specific signaling pathways associated with platinum resistance in ovarian cancer. *BMC medical genomics* 2, 34.
- Liang, C., Li, Y., Luo, J., Zhang, Z. (2015). A novel motif-discovery algorithm to identify co-regulatory motifs in large transcription factor and microRNA co-regulatory networks in human. *Bioinformatics* 31, 2348-2355.
- Lili, L.N., Matyunina, L.V., Walker, L., Benigno, B.B., McDonald, J.F. (2013). Molecular profiling predicts the existence of two functionally distinct classes of ovarian cancer stroma. *BioMed research international* 2013.
- Lin, C.-C., Chen, Y.-J., Chen, C.-Y., Oyang, Y.-J., Juan, H.-F., Huang, H.-C. (2012). Crosstalk between transcription factors and microRNAs in human protein interaction network. *BMC systems biology* 6, 18.
- Lin, Y., Cui, M., Shi, Y., Wang, F., Wang, Q., Teng, H. (2011). Increased COX-2 expression in patients with ovarian cancer. *African Journal of Biotechnology* 10, 15040-15043.
- Liu, E.T., Lauffenburger, D.A. (2009). Systems biomedicine: concepts and perspectives (Academic Press).
- Liu, N., Williams, A.H., Kim, Y., McAnally, J., Bezprozvannaya, S., Sutherland, L.B., Richardson, J.A., Bassel-Duby, R., Olson, E.N. (2007). An intragenic MEF2-dependent enhancer directs muscle-specific expression of microRNAs 1 and 133. *Proceedings of the National Academy of Sciences* 104, 20844-20849.
- Liu, S., Zhang, X., Shi, C., Lin, J., Chen, G., Wu, B., Wu, L., Shi, H., Yuan, Y., Zhou, W. (2015a). Altered microRNAs expression profiling in cumulus cells from

- patients with polycystic ovary syndrome. *Journal of translational medicine* 13, 238.
- Liu, Z.-P., Wu, C., Miao, H., Wu, H. (2015b). RegNetwork: an integrated database of transcriptional and post-transcriptional regulatory networks in human and mouse. *Database* 2015, bav095.
- Llauradó, M., Abal, M., Castellví, J., Cabrera, S., Gil-Moreno, A., Pérez-Benavente, A., Colás, E., Doll, A., Dolcet, X., Matias-Guiu, X. (2012). ETV5 transcription factor is overexpressed in ovarian cancer and regulates cell adhesion in ovarian cancer cells. *International journal of cancer* 130, 1532-1543.
- Llauradó, M., Abal, M., Castellví, J., Cabrera, S., Gil-Moreno, A., Pérez-Benavente, A., Colás, E., Doll, A., Dolcet, X., Matias-Guiu, X. (2012). ETV5 transcription factor is overexpressed in ovarian cancer and regulates cell adhesion in ovarian cancer cells. *International journal of cancer* 130, 1532-1543.
- López, Y., Nakai, K., Patil, A. (2015). HitPredict version 4: comprehensive reliability scoring of physical protein–protein interactions from more than 100 species. *Database: the journal of biological databases and curation* 2015.
- Lu, G., Zhang, Q., Huang, Y., Song, J., Tomaino, R., Ehrenberger, T., Lim, E., Liu, W., Bronson, R.T., Bowden, M. (2014). Phosphorylation of ETS1 by Src family kinases prevents its recognition by the COP1 tumor suppressor. *Cancer Cell* 26, 222-234.
- Lu, T.-P., Tsai, M.-H., Lee, J.-M., Hsu, C.-P., Chen, P.-C., Lin, C.-W., Shih, J.-Y., Yang, P.-C., Hsiao, C.K., Lai, L.-C. (2010). Identification of a novel biomarker SEMA5A for non-small cell lung carcinoma in non-smoking women. *Cancer Epidemiology and Prevention Biomarkers*, cebp. 0332.2010.
- Luvero, D., Milani, A., Ledermann, J.A. (2014). Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Therapeutic advances in medical oncology* 6, 229-239.
- Ma, R., Ye, X., Cheng, H., Ma, Y., Cui, H., Chang, X. (2015). PRSS3 expression is associated with tumor progression and poor prognosis in epithelial ovarian cancer. *Gynecologic oncology* 137, 546-552.
- Ma, Y., Ren, Y., Zhang, X., Lin, L., Liu, Y., Rong, F., Wen, W., Li, F. (2014). High GOLPH3 expression is associated with a more aggressive behavior of epithelial ovarian carcinoma. *Virchows Archiv* 464, 443-452.
- MacDonald, B.T., Tamai, K., He, X. (2009). Wnt/β-catenin signaling: components, mechanisms, and diseases. *Developmental cell* 17, 9-26.
- Maiuri, M.C., Kroemer, G. (2015). Essential role for oxidative phosphorylation in cancer progression. *Cell metabolism* 21, 11-12.
- Mangan, S., Alon, U. (2003). Structure and function of the feed-forward loop network motif. *Proceedings of the National Academy of Sciences* 100, 11980-11985.
- Manna, P.R., Stocco, D.M. (2011). The role of specific mitogen-activated protein kinase signaling cascades in the regulation of steroidogenesis. *Journal of signal transduction* 2011.
- Marchitti, S.A., Deitrich, R.A., Vasiliou, V. (2007). Neurotoxicity and metabolism of the catecholamine-derived 3, 4-dihydroxyphenylacetaldehyde and

- 3, 4-dihydroxyphenylglycolaldehyde: the role of aldehyde dehydrogenase. *Pharmacological reviews* 59, 125-150.
- Mardinoglu, A., Agren, R., Kampf, C., Asplund, A., Nookaew, I., Jacobson, P., Walley, A.J., Froguel, P., Carlsson, L.M., Uhlen, M. (2013). Integration of clinical data with a genome-scale metabolic model of the human adipocyte. *Molecular systems biology* 9, 649.
- Mardinoglu, A., Agren, R., Kampf, C., Asplund, A., Uhlen, M., Nielsen, J. (2014). Genome-scale metabolic modelling of hepatocytes reveals serine deficiency in patients with non-alcoholic fatty liver disease. *Nature communications* 5.
- Martinez, N.J., Walhout, A.J. (2009). The interplay between transcription factors and microRNAs in genome-scale regulatory networks. *Bioessays* 31, 435-445.
- McCubrey, J.A., Steelman, L.S., Chappell, W.H., Abrams, S.L., Wong, E.W., Chang, F., Lehmann, B., Terrian, D.M., Milella, M., Tafuri, A. (2007). Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1773, 1263-1284.
- McDonald, J., Bowen, N.J., Wang, L. (2014). MIR-200 family induces mesenchymal-to-epithelial transition (MET) in ovarian cancer cells (Google Patents).
- McMahon, H.T., Boucrot, E. (2011). Molecular mechanism and physiological functions of clathrin-mediated endocytosis. *Nature reviews Molecular cell biology* 12, 517-533.
- Mercer, T.R., Mattick, J.S. (2013). Understanding the regulatory and transcriptional complexity of the genome through structure. *Genome research* 23, 1081-1088.
- Merritt, M.A., Parsons, P.G., Newton, T.R., Martyn, A.C., Webb, P.M., Green, A.C., Papadimos, D.J., Boyle, G.M. (2009). Expression profiling identifies genes involved in neoplastic transformation of serous ovarian cancer. *BMC cancer* 9, 378.
- Miles, L., Miles, M.V., Tang, P.H., Horn, P.S., Quinlan, J.G., Wong, B., Wenisch, A., Bove, K.E. (2005). Ubiquinol: a potential biomarker for tissue energy requirements and oxidative stress. *Clinica chimica acta* 360, 87-96.
- Mills, E., O'Neill, L.A. (2014). Succinate: a metabolic signal in inflammation. *Trends in cell biology* 24, 313-320.
- Milne, K., Köbel, M., Kalloger, S.E., Barnes, R.O., Gao, D., Gilks, C.B., Watson, P.H., Nelson, B.H. (2013). Correction: Systematic Analysis of Immune Infiltrates in High-Grade Serous Ovarian Cancer Reveals CD20, FoxP3 and TIA-1 as Positive Prognostic Factors. *PLoS One* 8.
- Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., Alon, U. (2002). Network motifs: simple building blocks of complex networks. *Science* 298, 824-827.
- Mirzayans, R., Andrais, B., Scott, A., Murray, D. (2012). New insights into p53 signalling and cancer cell response to DNA damage: implications for cancer therapy. *BioMed Research International* 2012.

- Mitchell, T.J., John, S. (2005). Signal transducer and activator of transcription (STAT) signalling and T-cell lymphomas. *Immunology* 114, 301-312.
- Mitra, A.K., Zillhardt, M., Hua, Y., Tiwari, P., Murmann, A.E., Peter, M.E., Lengyel, E. (2012). MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer. *Cancer discovery* 2, 1100-1108.
- Mok, S.C., Bename, T., Vathipadiekal, V., Bell, A., Johnson, M.E., Park, D.-C., Hao, K., Yip, D.K., Donninger, H., Ozbun, L. (2009). A gene signature predictive for outcome in advanced ovarian cancer identifies a survival factor: microfibril-associated glycoprotein 2. *Cancer cell* 16, 521-532.
- Moreno, C.S., Matyunina, L., Dickerson, E.B., Schubert, N., Bowen, N.J., Logani, S., Benigno, B.B., McDonald, J.F. (2007). Evidence that p53-mediated cell-cycle-arrest inhibits chemotherapeutic treatment of ovarian carcinomas. *PLoS One* 2, e441.
- Morone, S., Lo-Buono, N., Parrotta, R., Giacomino, A., Nacci, G., Brusco, A., Larianov, A., Ostano, P., Mello-Grand, M., Chiorino, G. (2012). Overexpression of CD157 contributes to epithelial ovarian cancer progression by promoting mesenchymal differentiation. *PLoS One* 7, e43649.
- Mostowska, A., Pawlik, P., Sajdak, S., Markowska, J., Pawałowska, M., Lianeri, M., Jagodzinski, P.P. (2014). An analysis of polymorphisms within the Wnt signaling pathway in relation to ovarian cancer risk in a Polish population. *Molecular diagnosis & therapy* 18, 85-91.
- Moustakas, A., Pardali, K., Gaal, A., Heldin, C.-H. (2002). Mechanisms of TGF- β signaling in regulation of cell growth and differentiation. *Immunology letters* 82, 85-91.
- Mu, L., Zheng, W., Wang, L., Chen, X., Yang, J. (2008). Focal adhesion kinase expression in ovarian endometriosis. *International Journal of Gynecology & Obstetrics* 101, 161-165.
- Muller, P.A., Vousden, K.H. (2014). Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer cell* 25, 304-317.
- Munoz-Pinedo, C., El Mjiyad, N., Ricci, J. (2012). Cancer metabolism: current perspectives and future directions. *Cell death & disease* 3, e248.
- Nagaraj, N.S., Datta, P.K. (2010). Targeting the transforming growth factor- β signaling pathway in human cancer. *Expert opinion on investigational drugs* 19, 77-91.
- Nahum, G.G., Kaunitz, A.M., Rosen, K., Schmelter, T., Lynen, R. (2015). Ovarian cysts: presence and persistence with use of a 13.5 mg levonorgestrel-releasing intrauterine system. *Contraception* 91, 412-417.
- Nam, E.J., Lee, M., Yim, G.W., Kim, J.H., Kim, S., Kim, S.W., Kim, Y.T. (2012). MicroRNA profiling of a CD133+ spheroid-forming subpopulation of the OVCAR3 human ovarian cancer cell line. *BMC medical genomics* 5, 18.
- Neuberg, S.L., Kenrick, D.T., Schaller, M. (2011). Human threat management systems: Self-protection and disease avoidance. *Neuroscience & Biobehavioral Reviews* 35, 1042-1051.
- Ni, I.B.P., Zakaria, Z., Muhammad, R., Abdulla, N., Ibrahim, N., Emran, N.A., Abdulla, N.H., Hussain, S.N.A.S. (2010). Gene expression patterns distin-

- guish breast carcinomas from normal breast tissues: the Malaysian context. Pathology-Research and Practice 206, 223-228.
- Nicholas, M.K., Lukas, R.V., Jafri, N.F., Faoro, L., Salgia, R. (2006). Epidermal growth factor receptor-mediated signal transduction in the development and therapy of gliomas. Clinical Cancer Research 12, 7261-7270.
- Nishikawa, N., Toyota, M., Suzuki, H., Honma, T., Fujikane, T., Ohmura, T., Nishidate, T., Ohe-Toyota, M., Maruyama, R., Sonoda, T. (2007). Gene amplification and overexpression of PRDM14 in breast cancers. Cancer research 67, 9649-9657.
- Ntziachristos, P., Lim, J.S., Sage, J., Aifantis, I. (2014). From fly wings to targeted cancer therapies: a centennial for notch signaling. Cancer cell 25, 318-334.
- Nyman, D.W., Stratton, M.S., Kopplin, M.J., Dalkin, B.L., Nagle, R.B., Gandolfi, A.J. (2004). Selenium and selenomethionine levels in prostate cancer patients. Cancer detection and prevention 28, 8-16.
- Oksuz, Z., Serin, M.S., Kaplan, E., Dogen, A., Tezcan, S., Aslan, G., Emekdas, G., Sezgin, O., Altintas, E., Tiftik, E.N. (2015). Serum microRNAs; miR-30c-5p, miR-223-3p, miR-302c-3p and miR-17-5p could be used as novel non-invasive biomarkers for HCV-positive cirrhosis and hepatocellular carcinoma. Molecular biology reports 42, 713-720.
- Oksvold, M.P., Skarpen, E., Lindeman, B., Roos, N., Huitfeldt, H.S. (2000). Immunocytochemical localization of Shc and activated EGF receptor in early endosomes after EGF stimulation of HeLa cells. Journal of Histochemistry & Cytochemistry 48, 21-33.
- Ortega, I., Duleba, A.J. (2014). Role of Statins in PCOS Management. In Polycystic Ovary Syndrome (Springer), pp. 181-203.
- Pamuła-Piłat, J., Rubel, T., Rzepecka, I., Olbryt, M., Herok, R., Dansonka-Mieszkowska, A., Grzybowska, E., Kupryjańczyk, J. (2013). Gene expression profiles in three histologic types, clear-cell, endometrioid and serous ovarian carcinomas. Journal of biological regulators and homeostatic agents 28, 659-674.
- Panda, H., Pelakh, L., Chuang, T.-D., Luo, X., Bukulmez, O., Chegini, N. (2012). Endometrial miR-200c is altered during transformation into cancerous states and targets the expression of ZEBs, VEGFA, FLT1, IKK β , KLF9, and FBLN5. Reproductive sciences 19, 786-796.
- Papadatos-Pastos, D., Dedes, K.J., de Bono, J.S., Kaye, S.B. (2011). Revisiting the role of antiandrogen strategies in ovarian cancer. The oncologist 16, 1413-1421.
- Patil, K.R., Nielsen, J. (2005). Uncovering transcriptional regulation of metabolism by using metabolic network topology. Proc Natl Acad Sci U S A 102, 2685-2689.
- Paulsson, J., Micke, P. (2014). Prognostic relevance of cancer-associated fibroblasts in human cancer. Paper presented at: Seminars in cancer biology (Elsevier).
- Pavone, M.E., Lyttle, B.M. (2015). Endometriosis and ovarian cancer: links, risks, and challenges faced. International journal of women's health 7, 663.

- Peng, D.-X., Luo, M., Qiu, L.-W., He, Y.-L., Wang, X.-F. (2012). Prognostic implications of microRNA-100 and its functional roles in human epithelial ovarian cancer. *Oncology reports* 27, 1238-1244.
- Persico, M., Ceol, A., Gavrila, C., Hoffmann, R., Florio, A., Cesareni, G. (2005). HomoMINT: an inferred human network based on orthology mapping of protein interactions discovered in model organisms. *BMC bioinformatics* 6, S21.
- Petersen, C.P., Bordeleau, M.-E., Pelletier, J., Sharp, P.A. (2006). Short RNAs repress translation after initiation in mammalian cells. *Molecular cell* 21, 533-542.
- Pfister, T.D., Reinholt, W.C., Agama, K., Gupta, S., Khin, S.A., Kinders, R.J., Parchment, R.E., Tomaszewski, J.E., Doroshow, J.H., Pommier, Y. (2009). Topoisomerase I levels in the NCI-60 cancer cell line panel determined by validated ELISA and microarray analysis and correlation with indenoisoquinoline sensitivity. *Molecular cancer therapeutics* 8, 1878-1884.
- Pils, D., Bachmayr-Heyda, A., Auer, K., Svoboda, M., Auner, V., Hager, G., Obermayr, E., Reiner, A., Reinthaller, A., Speiser, P. (2014). Cyclin E1 (CCNE1) as independent positive prognostic factor in advanced stage serous ovarian cancer patients-A study of the OVCAD consortium. *European journal of cancer* 50, 99-110.
- Pink, R.C., Samuel, P., Massa, D., Caley, D.P., Brooks, S.A., Carter, D.R.F. (2015). The passenger strand, miR-21-3p, plays a role in mediating cisplatin resistance in ovarian cancer cells. *Gynecologic oncology* 137, 143-151.
- Plotnik, J.P., Budka, J.A., Ferris, M.W., Hollenhorst, P.C. (2014). ETS1 is a genome-wide effector of RAS/ERK signaling in epithelial cells. *Nucleic acids research* 42, 11928-11940.
- Pópolo, H., Lopes, J.M., Soares, P. (2012). The mTOR signalling pathway in human cancer. *International journal of molecular sciences* 13, 1886-1918.
- Porta, C., Paglino, C., Mosca, A. (2014). Targeting PI3K/Akt/mTOR signaling in cancer. *Targeting PI3K/mTOR signaling in cancer*, 47.
- Portales-Casamar, E., Arenillas, D., Lim, J., Swanson, M.I., Jiang, S., McCallum, A., Kirov, S., Wasserman, W.W. (2009). The PAZAR database of gene regulatory information coupled to the ORCA toolkit for the study of regulatory sequences. *Nucleic acids research* 37, D54-D60.
- Pralhada Rao, R., Vaidyanathan, N., Rengasamy, M., Mammen Oommen, A., Somaiya, N., Jagannath, M. (2013). Sphingolipid metabolic pathway: an overview of major roles played in human diseases. *Journal of lipids* 2013.
- Prasad, T.K., Goel, R., Kandasamy, K., Keerthikumar, S., Kumar, S., Mathivanan, S., Telikicherla, D., Raju, R., Shafreen, B., Venugopal, A. (2009). Human protein reference database—2009 update. *Nucleic acids research* 37, D767-D772.
- Prat, J. (2014). Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *International Journal of Gynecology & Obstetrics* 124, 1-5.
- Pundir, C.S., Devi, R. (2014). Biosensing methods for xanthine determination: A review. *Enzyme and microbial technology* 57, 55-62.

- Qiu, C., Wang, J., Yao, P., Wang, E., Cui, Q. (2010). microRNA evolution in a human transcription factor and microRNA regulatory network. *BMC systems biology* 4, 90.
- Quail, D.F., Joyce, J.A. (2013). Microenvironmental regulation of tumor progression and metastasis. *Nature medicine* 19, 1423-1437.
- Ravichandran, K.S. (2001). Signaling via Shc family adapter proteins. *Oncogene* 20, 6322.
- Richards, J.S., Pangas, S.A. (2010). The ovary: basic biology and clinical implications. *The Journal of clinical investigation* 120, 963-972.
- Ritchie, W., Granjeaud, S., Puthier, D., Gautheret, D. (2008). Entropy measures quantify global splicing disorders in cancer. *PLoS Comput Biol* 4, e1000011.
- Ross, D.T., Scherf, U., Eisen, M.B., Perou, C.M., Rees, C., Spellman, P., Iyer, V., Jeffrey, S.S., Van de Rijn, M., Waltham, M. (2000). Systematic variation in gene expression patterns in human cancer cell lines. *Nature genetics* 24, 227-235.
- Sampson, J.A. (1925). Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. *Archives of Surgery* 10, 1-72.
- Sayasneh, A., Tsivios, D., Crawford, R. (2011). Endometriosis and ovarian cancer: a systematic review. *ISRN obstetrics and gynecology* 2011.
- Schaefer, M.H., Fontaine, J.-F., Vinayagam, A., Porras, P., Wanker, E.E., Andrade-Navarro, M.A. (2012). HIPPIE: Integrating protein interaction networks with experiment based quality scores. *PLoS One* 7, e31826.
- Schauer, I.G., Sood, A.K., Mok, S., Liu, J. (2011). Cancer-associated fibroblasts and their putative role in potentiating the initiation and development of epithelial ovarian cancer. *Neoplasia* 13, 393-405.
- Scotto, L., Narayan, G., Nandula, S.V., Arias-Pulido, H., Subramaniyam, S., Schneider, A., Kaufmann, A.M., Wright, J.D., Pothuri, B., Mansukhani, M. (2008). Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: potential role in progression. *Genes, Chromosomes and Cancer* 47, 755-765.
- Sedlák, E., Fabian, M., Robinson, N.C., Musatov, A. (2010). Ferricytochrome c protects mitochondrial cytochrome c oxidase against hydrogen peroxide-induced oxidative damage. *Free Radical Biology and Medicine* 49, 1574-1581.
- Sengupta, D., Bandyopadhyay, S. (2013). Topological patterns in microRNA–gene regulatory network: studies in colorectal and breast cancer. *Molecular bioSystems* 9, 1360-1371.
- Sevimoglu, T., Arga, K.Y. (2014). The role of protein interaction networks in systems biomedicine. *Computational and structural biotechnology journal* 11, 22-27.
- Sevimoglu, T., Arga, K.Y. (2015). Computational systems biology of psoriasis: Are we ready for the age of omics and systems biomarkers? *Omics: a journal of integrative biology* 19, 669-687.
- Shahab, S.W., Matyunina, L.V., Mezencev, R., Walker, L.D., Bowen, N.J., Benigno, B.B., McDonald, J.F. (2011). Evidence for the complexity of microRNA-mediated regulation in ovarian cancer: a systems approach. *PLoS One* 6, e22508.

- Shalgi, R., Lieber, D., Oren, M., Pilpel, Y. (2007). Global and local architecture of the mammalian microRNA–transcription factor regulatory network. PLoS Comput Biol 3, e131.
- Shen-Orr, S.S., Milo, R., Mangan, S., Alon, U. (2002). Network motifs in the transcriptional regulation network of Escherichia coli. Nature genetics 31, 64-68.
- Shenouda, S.K., Alahari, S.K. (2009). MicroRNA function in cancer: oncogene or a tumor suppressor? Cancer and Metastasis Reviews 28, 369.
- Shi, Y., Massagué, J. (2003). Mechanisms of TGF- β signaling from cell membrane to the nucleus. Cell 113, 685-700.
- Shields, B.B., Pecot, C.V., Gao, H., McMillan, E., Potts, M., Nagel, C., Purinton, S., Wang, Y., Ivan, C., Kim, H.S. (2015). A genome-scale screen reveals context-dependent ovarian cancer sensitivity to miRNA overexpression. Molecular systems biology 11, 842.
- Shlomi, T., Cabili, M.N., Herrgård, M.J., Palsson, B.Ø., Ruppin, E. (2008). Network-based prediction of human tissue-specific metabolism. Nature biotechnology 26, 1003-1010.
- Siegel, R.L., Miller, K.D., Jemal, A. (2016). Cancer statistics, 2016. CA: a cancer journal for clinicians 66, 7-30.
- Signorile, P.G., Baldi, A. (2015). New evidence in endometriosis. The international journal of biochemistry & cell biology 60, 19-22.
- Simoens, S., Hummelshoj, L., D'Hooghe, T. (2007). Endometriosis: cost estimates and methodological perspective. Human reproduction update 13, 395-404.
- Sims, A., Zweemer, A.J., Nagumo, Y., Faratian, D., Muir, M., Dodds, M., Um, I., Kay, C., Hasmann, M., Harrison, D. (2012). Defining the molecular response to trastuzumab, pertuzumab and combination therapy in ovarian cancer. British journal of cancer 106, 1779-1789.
- Siu, K.T., Rosner, M.R., Minella, A.C. (2012). An integrated view of cyclin E function and regulation. Cell cycle 11, 57-64.
- Smoot, M.E., Ono, K., Ruscheinski, J., Wang, P.-L., Ideker, T. (2011). Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics 27, 431-432.
- Smyth, G.K., Ritchie, M., Thorne, N., Wettenhall, J. (2005). LIMMA: linear models for microarray data. In Bioinformatics and Computational Biology Solutions Using R and Bioconductor. Statistics for Biology and Health.
- Solomon, D.A., Kim, T., Diaz-Martinez, L.A., Fair, J., Elkahloun, A.G., Harris, B.T., Toretsky, J.A., Rosenberg, S.A., Shukla, N., Ladanyi, M. (2011). Mutational inactivation of STAG2 causes aneuploidy in human cancer. Science 333, 1039-1043.
- Sørensen, A.E., Wissing, M.L., Salö, S., Englund, A.L.M., Dalgaard, L.T. (2014). MicroRNAs related to polycystic ovary syndrome (PCOS). Genes 5, 684-708.
- Sourbier, C., Ricketts, C.J., Matsumoto, S., Crooks, D.R., Liao, P.-J., Mannes, P.Z., Yang, Y., Wei, M.-H., Srivastava, G., Ghosh, S. (2014). Targeting ABL1-mediated oxidative stress adaptation in fumarate hydratase-deficient cancer. Cancer Cell 26, 840-850.

- Spillman, M.A., Manning, N.G., Dye, W.W., Sartorius, C.A., Post, M.D., Harrell, J.C., Jacobsen, B.M., Horwitz, K.B. (2010). Tissue-specific pathways for estrogen regulation of ovarian cancer growth and metastasis. *Cancer research* 70, 8927-8936.
- Stegh, A.H. (2012). Targeting the p53 signaling pathway in cancer therapy—the promises, challenges and perils. *Expert opinion on therapeutic targets* 16, 67-83.
- Stevens, V.L., McCullough, M.L., Pavluck, A.L., Talbot, J.T., Feigelson, H.S., Thun, M.J., Calle, E.E. (2007). Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence. *Cancer Epidemiology and Prevention Biomarkers* 16, 1140-1147.
- Stoppa-Lyonnet, D. (2016). The biological effects and clinical implications of BRCA mutations: where do we go from here? *European Journal of Human Genetics* 24, S3-S9.
- Stuart, J.M., Segal, E., Koller, D., Kim, S.K. (2003). A gene-coexpression network for global discovery of conserved genetic modules. *Science* 302, 249-255.
- Stuckey, A., Fischer, A., Miller, D.H., Hillenmeyer, S., Kim, K.K., Ritz, A., Singh, R.K., Raphael, B.J., Brard, L., Brodsky, A.S. (2011). Integrated genomics of ovarian xenograft tumor progression and chemotherapy response. *BMC cancer* 11, 308.
- Sun, B., Jiang, H. (2012). An efficient approach for total synthesis of aminopropyl functionalized ganglioside GM1b. *Tetrahedron Letters* 53, 5711-5715.
- Sun, F., Ding, W., He, J.-H., Wang, X.-J., Ma, Z.-B., Li, Y.-F. (2015). Stomatin-like protein 2 is overexpressed in epithelial ovarian cancer and predicts poor patient survival. *BMC cancer* 15, 746.
- Sun, J., Gong, X., Purow, B., Zhao, Z. (2012). Uncovering microRNA and transcription factor mediated regulatory networks in glioblastoma. *PLoS Comput Biol* 8, e1002488.
- Sun, S.-Y., Liu, Z.-P., Zeng, T., Wang, Y., Chen, L. (2013). Spatio-temporal analysis of type 2 diabetes mellitus based on differential expression networks. *Scientific reports* 3, 2268.
- Suzuki, H.I., Yamagata, K., Sugimoto, K., Iwamoto, T., Kato, S., Miyazono, K. (2009). Modulation of microRNA processing by p53. *Nature* 460, 529-533.
- Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., Simonovic, M., Roth, A., Santos, A., Tsafou, K.P. (2014). STRING v10: protein–protein interaction networks, integrated over the tree of life. *Nucleic acids research*, gku1003.
- Teplinsky, E., Muggia, F. (2015). EGFR and HER2: is there a role in ovarian cancer? *Translational Cancer Research* 4, 107-117.
- Teschendorff, A.E., Banerji, C.R., Severini, S., Kuehn, R., Sollich, P. (2015). Increased signaling entropy in cancer requires the scale-free property of protein interaction networks. *Scientific reports* 5.
- Tessneer, K.L., Cai, X., Pasula, S., Dong, Y., Liu, X., Chang, B., McManus, J., Hahn, S., Yu, L., Chen, H. (2013). Epsin family of endocytic adaptor proteins as on-

- cogenic regulators of cancer progression. *Journal of cancer research updates* 2, 144.
- Thériault, B.L., Pajovic, S., Bernardini, M.Q., Shaw, P.A., Gallie, B.L. (2012). Kininsin family member 14: an independent prognostic marker and potential therapeutic target for ovarian cancer. *International journal of cancer* 130, 1844-1854.
- Thiele, I., Swainston, N., Fleming, R.M., Hoppe, A., Sahoo, S., Aurich, M.K., Haraldsdottir, H., Mo, M.L., Rolfsson, O., Stobbe, M.D. (2013). A community-driven global reconstruction of human metabolism. *Nature biotechnology* 31, 419-425.
- Tian, M., Neil, J.R., Schiemann, W.P. (2011). Transforming growth factor- β and the hallmarks of cancer. *Cellular signalling* 23, 951-962.
- Tillinghast, G.W., Partee, J., Albert, P., Kelley, J.M., Burtow, K.H., Kelly, K. (2003). Analysis of genetic stability at the EP300 and CREBBP loci in a panel of cancer cell lines. *Genes, Chromosomes and Cancer* 37, 121-131.
- Todeschini, A.-L., Georges, A., Veitia, R.A. (2014). Transcription factors: specific DNA binding and specific gene regulation. *Trends in genetics* 30, 211-219.
- Tsang, J., Zhu, J., van Oudenaarden, A. (2007). MicroRNA-mediated feedback and feedforward loops are recurrent network motifs in mammals. *Molecular cell* 26, 753-767.
- Tseng, G.C., Ghosh, D., Feingold, E. (2012). Comprehensive literature review and statistical considerations for microarray meta-analysis. *Nucleic acids research*, gkr1265.
- Tung, C.S., Mok, S.C., Tsang, Y.T., Zu, Z., Song, H., Liu, J., Deavers, M.T., Malpica, A., Wolf, J.K., Lu, K.H. (2009). PAX2 expression in low malignant potential ovarian tumors and low-grade ovarian serous carcinomas. *Modern Pathology* 22, 1243-1250.
- Uhlén, M., Fagerberg, L., Hallström, B.M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, Å., Kampf, C., Sjöstedt, E., Asplund, A. (2015). Tissue-based map of the human proteome. *Science* 347, 1260419.
- Varadan, V., Anastassiou, D. (2006). Inference of disease-related molecular logic from systems-based microarray analysis. *PLoS Comput Biol* 2, e68.
- Vargova, K., Curik, N., Burda, P., Basova, P., Kuvait, V., Pospisil, V., Savvulidi, F., Kokavec, J., Necas, E., Berkova, A. (2011). MYB transcriptionally regulates the miR-155 host gene in chronic lymphocytic leukemia. *Blood* 117, 3816-3825.
- Vasudevan, S., Tong, Y., Steitz, J.A. (2007). Switching from repression to activation: microRNAs can up-regulate translation. *Science* 318, 1931-1934.
- Vathipadiekal, V., Wang, V., Wei, W., Waldron, L., Drapkin, R., Gillette, M., Skates, S., Birrer, M. (2015). Creation of a Human Secretome: A Novel Composite Library of Human Secreted Proteins: Validation Using Ovarian Cancer Gene Expression Data and a Virtual Secretome Array. *Clinical Cancer Research* 21, 4960-4969.
- Vazquez, A., Liu, J., Zhou, Y., Oltvai, Z.N. (2010). Catabolic efficiency of aerobic glycolysis: the Warburg effect revisited. *BMC systems biology* 4, 58.

- Vouk, K., Hevir, N., Ribič-Pucelj, M., Haarpaintner, G., Scherb, H., Osredkar, J., Möller, G., Prehn, C., Rižner, T.L., Adamski, J. (2012). Discovery of phosphatidylcholines and sphingomyelins as biomarkers for ovarian endometriosis. *Human Reproduction*, des152.
- Vousden, K.H., Prives, C. (2009). Blinded by the light: the growing complexity of p53. *Cell* 137, 413-431.
- Walley, A., Jacobson, P., Falchi, M., Bottolo, L., Andersson, J., Petretto, E., Bonnefond, A., Vaillant, E., Lecoeur, C., Vatin, V. (2012). Differential coexpression analysis of obesity-associated networks in human subcutaneous adipose tissue. *International journal of obesity* 36, 137-147.
- Wang, B., Love, T.M., Call, M.E., Doench, J.G., Novina, C.D. (2006). Recapitulation of short RNA-directed translational gene silencing in vitro. *Molecular cell* 22, 553-560.
- Wang, H.-L., Lu, R.-Q., Xie, S.-H., Zheng, H., Wen, X.-M., Gao, X., Guo, L. (2015). SIRT7 exhibits oncogenic potential in human ovarian cancer cells. *Asian Pac J Cancer Prev* 16, 3573-3577.
- Wang, J., Duncan, D., Shi, Z., Zhang, B. (2013). WEB-based gene set analysis toolkit (WebGestalt): update 2013. *Nucleic acids research* 41, W77-W83.
- Wang, J., Lu, M., Qiu, C., Cui, Q. (2010). TransmiR: a transcription factor-miRNA regulation database. *Nucleic acids research* 38, D119-D122.
- Wang, S., Zhang, S. (2011). Dickkopf-1 is frequently overexpressed in ovarian serous carcinoma and involved in tumor invasion. *Clinical & experimental metastasis* 28, 581-591.
- Wang, X. (2008). miRDB: a microRNA target prediction and functional annotation database with a wiki interface. *Rna* 14, 1012-1017.
- Wang, Y., Chen, L., Wu, Z., Wang, M., Jin, F., Wang, N., Hu, X., Liu, Z., Zhang, C.-Y., Zen, K. (2016). miR-124-3p functions as a tumor suppressor in breast cancer by targeting CBL. *BMC cancer* 16, 826.
- Wang, Y., Eddy, J.A., Price, N.D. (2012). Reconstruction of genome-scale metabolic models for 126 human tissues using mCADRE. *BMC systems biology* 6, 153.
- Warsow, G., Struckmann, S., Kerkhoff, C., Reimer, T., Engel, N., Fuellen, G. (2013). Differential network analysis applied to preoperative breast cancer chemotherapy response. *PLoS One* 8, e81784.
- Wernicke, S. (2006). Efficient detection of network motifs. *IEEE/ACM Transactions on Computational Biology and Bioinformatics* 3.
- West, J., Bianconi, G., Severini, S., Teschendorff, A.E. (2012). Differential network entropy reveals cancer system hallmarks. *Scientific reports* 2, 802.
- Whitworth, J.M., Londoño-Joshi, A.I., Sellers, J.C., Oliver, P.J., Muccio, D.D., Atigadda, V.R., Straughn, J.M., Buchsbaum, D.J. (2012). The impact of novel retinoids in combination with platinum chemotherapy on ovarian cancer stem cells. *Gynecologic oncology* 125, 226-230.
- Willis, S., Villalobos, V.M., Gevaert, O., Abramovitz, M., Williams, C., Sikic, B.I., Leyland-Jones, B. (2016). Single gene prognostic biomarkers in ovarian cancer: A meta-analysis. *PLoS One* 11, e0149183.

- Wilson, A.C., Vadakkadath Meethal, S., Bowen, R.L., Atwood, C.S. (2007). Leuprolide acetate: a drug of diverse clinical applications. Expert opinion on investigational drugs 16, 1851-1863.
- Wolf, D.M., Lenburg, M.E., Yau, C., Boudreau, A., van't Veer, L.J. (2014). Gene co-expression modules as clinically relevant hallmarks of breast cancer diversity. PLoS One 9, e88309.
- Wong, R.R., Chan, L.K., Tsang, T.P., Lee, C.W., Cheung, T., Yim, S., Siu, N.S., Lee, S.N., Yu, M., Chim, S.S. (2011). CHD5 downregulation associated with poor prognosis in epithelial ovarian cancer. Gynecologic and obstetric investigation 72, 203-207.
- Wood, J.R., Nelson-Degrave, V.L., Jansen, E., McAllister, J.M., Mosselman, S., Strauss, J.F. (2005). Valproate-induced alterations in human theca cell gene expression: clues to the association between valproate use and metabolic side effects. Physiological genomics 20, 233-243.
- Xi, Q., Huang, M., Wang, Y., Zhong, J., Liu, R., Xu, G., Jiang, L., Wang, J., Fang, Z., Yang, S. (2015). The expression of CDK1 is associated with proliferation and can be a prognostic factor in epithelial ovarian cancer. Tumor Biology 36, 4939-4948.
- Xia, J., Rocke, D.M., Perry, G., Ray, M. (2014). Differential network analyses of Alzheimer's disease identify early events in Alzheimer's disease pathology. International Journal of Alzheimer's Disease 2014.
- Xiao, F., Zuo, Z., Cai, G., Kang, S., Gao, X., Li, T. (2009). miRecords: an integrated resource for microRNA-target interactions. Nucleic acids research 37, D105-D110.
- Xiong, J., Liu, J., Rayner, S., Li, Y., Chen, S. (2010). Protein-protein interaction reveals synergistic discrimination of cancer phenotype. Cancer informatics 9, 61.
- Xu, X., Li, S., Lin, Y., Chen, H., Hu, Z., Mao, Y., Xu, X., Wu, J., Zhu, Y., Zheng, X. (2013). MicroRNA-124-3p inhibits cell migration and invasion in bladder cancer cells by targeting ROCK1. Journal of translational medicine 11, 276.
- Xue, J., Lin, X., Chiu, W.-T., Chen, Y.-H., Yu, G., Liu, M., Feng, X.-H., Sawaya, R., Medema, R.H., Hung, M.-C. (2014). Sustained activation of SMAD3/SMAD4 by FOXM1 promotes TGF- β -dependent cancer metastasis. The Journal of clinical investigation 124, 564-579.
- Yang, D., Sun, Y., Hu, L., Zheng, H., Ji, P., Pecot, C.V., Zhao, Y., Reynolds, S., Cheng, H., Rupaimoole, R. (2013). Integrated analyses identify a master microRNA regulatory network for the mesenchymal subtype in serous ovarian cancer. Cancer cell 23, 186-199.
- Yang, H., Kong, W., He, L., Zhao, J.-J., O'Donnell, J.D., Wang, J., Wenham, R.M., Coppola, D., Kruk, P.A., Nicosia, S.V. (2008). MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. Cancer research 68, 425-433.
- Yang, J.-H., Li, J.-H., Shao, P., Zhou, H., Chen, Y.-Q., Qu, L.-H. (2011). starBase: a database for exploring microRNA-mRNA interaction maps from Argonaute CLIP-Seq and Degradome-Seq data. Nucleic acids research 39, D202-D209.

- Yang, L., Li, N., Wang, H., Jia, X., Wang, X., Luo, J. (2012). Altered microRNA expression in cisplatin-resistant ovarian cancer cells and upregulation of miR-130a associated with MDR1/P-glycoprotein-mediated drug resistance. *Oncology reports* 28, 592-600.
- Yang, Y., Hou, N., Wang, X., Wang, L., He, K., Zhao, Z., Zhao, X., Song, T., Huang, C. (2015). miR-15b-5p induces endoplasmic reticulum stress and apoptosis in human hepatocellular carcinoma, both in vitro and in vivo, by suppressing Rab1A. *Oncotarget* 6, 16227-16238.
- Yang, Z., He, M., Wang, K., Sun, G., Tang, L., Xu, Z. (2014). Tumor suppressive microRNA-193b promotes breast cancer progression via targeting DNAJC13 and RAB22A. *Int J Clin Exp Pathol* 7, 7563-7570.
- Ye, X., Chun, J. (2010). Lysophosphatidic acid (LPA) signaling in vertebrate reproduction. *Trends in Endocrinology & Metabolism* 21, 17-24.
- Yeung, T.-L., Leung, C.S., Wong, K.-K., Samimi, G., Thompson, M.S., Liu, J., Zaid, T.M., Ghosh, S., Birrer, M.J., Mok, S.C. (2013). TGF- β modulates ovarian cancer invasion by upregulating CAF-derived versican in the tumor microenvironment. *Cancer research* 73, 5016-5028.
- Yu, H., Gerstein, M. (2006). Genomic analysis of the hierarchical structure of regulatory networks. *Proceedings of the National Academy of Sciences* 103, 14724-14731.
- Yu, H., Tu, K., Wang, Y.-J., Mao, J.-Z., Xie, L., Li, Y.-Y., Li, Y.-X. (2012a). Combinatorial network of transcriptional regulation and microRNA regulation in human cancer. *BMC systems biology* 6, 61.
- Yu, X., Lin, J., Zack, D.J., Mendell, J.T., Qian, J. (2008). Analysis of regulatory network topology reveals functionally distinct classes of microRNAs. *Nucleic acids research* 36, 6494-6503.
- Yu, X., Vazquez, A., Levine, A.J., Carpizo, D.R. (2012b). Allele-specific p53 mutant reactivation. *Cancer cell* 21, 614-625.
- Zhang, B., Pan, X., Cobb, G.P., Anderson, T.A. (2007). microRNAs as oncogenes and tumor suppressors. *Developmental biology* 302, 1-12.
- Zhang, G., He, P., Tan, H., Budhu, A., Gaedcke, J., Ghadimi, B.M., Ried, T., Yfantidis, H.G., Lee, D.H., Maitra, A. (2013a). Integration of metabolomics and transcriptomics revealed a fatty acid network exerting growth inhibitory effects in human pancreatic cancer. *Clinical cancer research* 19, 4983-4993.
- Zhang, H., Qiu, J., Ye, C., Yang, D., Gao, L., Su, Y., Tang, X., Xu, N., Zhang, D., Xiong, L. (2014a). ROR1 expression correlated with poor clinical outcome in human ovarian cancer. *Scientific reports* 4, 5811.
- Zhang, J., Song, Y., Zhang, C., Zhi, X., Fu, H., Ma, Y., Chen, Y., Pan, F., Wang, K., Ni, J. (2015). Circulating MiR-16-5p and MiR-19b-3p as two novel potential biomarkers to indicate progression of gastric cancer. *Theranostics* 5, 733.
- Zhang, J., Xiang, Y., Ding, L., Borlawsky, T.B., Ozer, H.G., Jin, R., Payne, P., Huang, K. (2010). Using gene co-expression network analysis to predict biomarkers for chronic lymphocytic leukemia. *BMC bioinformatics* 11, S5.
- Zhang, L., Liu, W., Hao, Q., Bao, L., Wang, K. (2012). Folate intake and methylenetetrahydrofolate reductase gene polymorphisms as predictive and prog-

- nostic biomarkers for ovarian cancer risk. International journal of molecular sciences 13, 4009-4020.
- Zhang, Q., Burdette, J.E., Wang, J.-P. (2014b). Integrative network analysis of TCGA data for ovarian cancer. BMC systems biology 8, 1338.
- Zhang, W., Ota, T., Shridhar, V., Chien, J., Wu, B., Kuang, R. (2013b). Network-based survival analysis reveals subnetwork signatures for predicting outcomes of ovarian cancer treatment. PLoS Comput Biol 9, e1002975.
- Zhang, X.-F., Ou-Yang, L., Zhao, X.-M., Yan, H. (2016). Differential network analysis from cross-platform gene expression data. Scientific Reports 6.
- Zhou, Y., Ferguson, J., Chang, J.T., Kluger, Y. (2007). Inter-and intra-combinatorial regulation by transcription factors and microRNAs. BMC genomics 8, 396.
- Zhou, Y., Liu, Y., Li, K., Zhang, R., Qiu, F., Zhao, N., Xu, Y. (2015). ICan: an integrated co-alteration network to identify ovarian cancer-related genes. PLoS One 10, e0116095.
- Zhu, H., Yu, J.J. (2010). Gene expression patterns in the histopathological classification of epithelial ovarian cancer. Experimental and therapeutic medicine 1, 187-192.
- Zickenrott, S., Angarica, V., Upadhyaya, B., Del Sol, A. (2016). Prediction of disease–gene–drug relationships following a differential network analysis. Cell death & disease 7, e2040.