## L1000 viewer: A search engine and Web interface for the LINCS data repository

The LINCS L1000 data repository contains almost two million gene expression profiles for thousands of small molecules and drugs. However, due to the complexity and the size of the data repository and a lack of an interoperable interface, the creation of pharmacologically meaningful workflows utilizing these data is severely hampered. In order to overcome this limitation, we developed the L1000 Viewer, a search engine and graphical web interface for the LINCS data repository. The web interface serves as an interactive platform allowing the user to select different forms of perturbation profiles, e.g., for specific cell lines, drugs, dosages, time points and combinations thereof. At its core, our method has a database we created from inferring and utilizing the intricate dependency graph structure among the data files. The L1000 Viewer is accessible via http://L1000viewer.bio-complexity.com/.

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Contributors: Musa, A., Tripathi, S., Dehmer, M., Emmert-Streib, F.
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## Prostate cancer gene regulatory network inferred from RNA-seq data

Background: Cancer is a complex disease with a lucid etiology and in understanding the causation, we need to appreciate this complexity. Objective: Here we are aiming to gain insights into the genetic associations of prostate cancer through a network-based systems approach using the BC3Net algorithm. Methods: Specifically, we infer a prostate cancer Gene Regulatory Network (GRN) from a large-scale gene expression data set of 333 patient RNA-seq profiles obtained from The Cancer Genome Atlas (TCGA) database. Results: We analyze the functional components of the inferred network by extracting subnetworks based on biological process information and interpret the role of known cancer genes within each process. Furthermore, we investigate the local landscape of prostate cancer genes and discuss pathological associations that may be relevant in the development of new targeted cancer therapies. Conclusion: Our network-based analysis provides a practical systems biology approach to reveal the collective gene-interactions of prostate cancer. This allows a close interpretation of biological activity in terms of the hallmarks of cancer.

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Contributors: Moore, D., Simoes, R. D. M., Dehmer, M., Emmert-Streib, F.
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**In a quest for engineering acidophiles for biomining applications: Challenges and opportunities**

Biomining with acidophilic microorganisms has been used at commercial scale for the extraction of metals from various sulfide ores. With metal demand and energy prices on the rise and the concurrent decline in quality and availability of mineral resources, there is an increasing interest in applying biomining technology, in particular for leaching metals from low grade minerals and wastes. However, bioprocessing is often hampered by the presence of inhibitory compounds that originate from complex ores. Synthetic biology could provide tools to improve the tolerance of biomining microbes to various stress factors that are present in biomining environments, which would ultimately increase bioleaching efficiency. This paper reviews the state-of-the-art tools to genetically modify acidophilic biomining microorganisms and the limitations of these tools. The first part of this review discusses resilience pathways that can be engineered in acidophiles to enhance their robustness and tolerance in harsh environments that prevail in bioleaching. The second part of the paper reviews the efforts that have been carried out towards engineering robust microorganisms and developing metabolic modelling tools. Novel synthetic biology tools have the potential to transform the biomining industry and facilitate the extraction of value from ores and wastes that cannot be processed with existing biomining microorganisms.

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MoE publication type: A2 Review article in a scientific journal
Organisations: Chemistry and Bioengineering, Research group: Bio- and Circular Economy, CSIRO Energy Centre, Montana State University (MSU), School of Pathology and Laboratory Medicine, University of Western Australia
Contributors: Gumulya, Y., Boxall, N. J., Khaleque, H. N., Santala, V., Carlson, R. P., Kaksonen, A. H.
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## Lessons from the human genome project: Modesty, honesty, and realism

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Contributors: Emmert-Streib, F., Dehmer, M., Yli-Harja, O.
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## Against dataism and for data sharing of big biomedical and clinical data with research parasites

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Organisations: Department of Signal Processing, Research group: Computational Systems Biology, Laboratory of Biosystem Dynamics, Nankai University
Contributors: Emmert-Streib, F., Dehmer, M., Yli-Harja, O.
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### The need for formally defining "modern medicine" by means of experimental design

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Organisations: Department of Signal Processing, Research group: Computational Systems Biology
Contributors: Emmert-Streib, F., Tuomisto, L., Yli-Harja, O.
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### Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans
Genome-wide association studies (GWAS) have identified numerouscommon prostate cancer (PrCa) susceptibility loci. We have fine-mapped 64 GWAS regions known at the conclusion of the iCOGS study using large-scale genotyping and imputation in 25 723 PrCa cases and 26 274 controls of European ancestry. We detected evidence for multiple independent signals at 16 regions, 12 of which contained additional newly identified significant associations. A single signal comprising a spectrum of correlated variationwas observed at 39 regions; 35 of which are nowdescribed by a novel more significantly associated lead SNP, while the originally reported variant remained as the lead SNP only in 4 regions. We also confirmed two association signals in Europeans that had been previously reported only in East-AsianGWAS. Based on statistical evidence and linkage disequilibrium (LD) structure, we have curated and narrowed down the list of the most likely candidate causal variants for each region. Functional annotation using data from ENCODE filtered for PrCa cell lines and eQTL analysis demonstrated significant enrichment for overlap with bio-features within this set. By incorporating the novel risk variants identified here alongside the refined data for existing association signals, we estimate that these loci nowexplain ~38.9% of the familial relative risk of PrCa, an 8.9% improvement over the previously reportedGWAS tag SNPs. This suggests that a significant fraction of the heritability of PrCa may have been hidden during the discovery phase of GWAS, in particular due to the presence of multiple independent signals within the same region.

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Medical University–Sofia, Queensland University of Technology QUT, QIMR Berghofer Medical Research Institute, Univ Porto, Universidade do Porto, Fac Med, Dept Med Imaging, IPO-Porto, University of Surrey, Warwick Medical School, King's College London, Universite de Geneve, Dana-Farber Cancer Institute, Department of Urology
Contributors: Al Olama, A. A., Dadaev, T., Hazelett, D. J., Li, Q., Leongamornlert, D., Saunders, E. J., Stephens, S., Cieza-Borrella, C., Whitmore, I., Garcia, S. B., Giles, G. G., Southey, M. C., Fitzgerald, L., Gronberg, H., Wiklund, F., Aly, M., Henderson, B. E., Schumacher, F., Haiman, C. A., Schleutker, J., Wahlfors, T., Tammela, T. L., Nordestgaard, B. G., Key, T. J., Travis, R. C., Neal, D. E., Donovan, J. L., Hamdy, F. C., Pharoah, P., Pashayan, N., Khaw, K. T., Stanford, J. L., Thibodeau, S. N., Mcdonnell, S. K., Schaid, D. J., Maier, C., Vogel, W., Luedeke, M., Herkommer, K., Kibel, A. S., Cybulski, C., Wokolorczyk, D., Kluzniak, W., Cannon-Albright, L., Brenner, H., Butterbach, K., Arndt, V., Park, J. Y., Sellers, T., Lin, H. Y., Slavov, C., Kaneva, R., Mitev, V., Batra, J., Clements, J. A., Spurdle, A., Teixeira, M. R., Paulo, P., Maia, S., Pandha, H., Michael, A., Kierzek, A., Govindasami, K., Guy, M., Lophatonanon, A., Muir, K., Viñuela, A., Brown, A. A., Freedman, M., Conti, D. V., Easton, D., Coetzee, G. A., Eeles, R. A., Kote-Jarai, Z.
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**A genome-wide expression quantitative trait loci analysis of proprotein convertase subtilisin/kexin enzymes identifies a novel regulatory gene variant for FURIN expression and blood pressure**
Proprotein convertase subtilisin/kexin (PCSK) enzymes cleave and convert their immature substrates into biologically active forms. Polymorphisms in the PCSK genes have been reported to associate with human diseases and phenotypes, including hypercholesterolemia and blood pressure (BP), and targeting PCSKs is considered a promising future form of drug therapy. PCSK processing is readily induced upon upregulation of the enzyme, but the genetic factors contributing to PCSK expression have not been thoroughly characterized. To gain a comprehensive understanding of the genetic regulation of PCSK expression, we performed, for the first time, a genome-wide expression quantitative trait loci (eQTL) analysis using mRNA expression in >1400 human peripheral blood samples from the Cardiovascular Risk in Young Finns Study and ca. ten million single-nucleotide polymorphisms (SNPs). The expression data showed clear expression for FURIN, PCSK5, PCSK7 and MBTPS1 (membrane-bound transcription factor peptidase, site 1) mRNAs in virtually all tested samples. A discovery analysis demonstrated a genome-wide significant ($p < 10^{-8}$) association with the selected PCSK probes for 1024 variants, which were located at ten independent loci. Of these loci, 5/10 could be confirmed to regulate PCSK expression in two additional and independent sample sets. Finally, a phenotypic analysis demonstrated that a novel cis-eQTL SNP rs4702 for FURIN is strongly associated with both diastolic ($p = 0.012$) and systolic ($p = 0.035$) BP levels, as well as peripheral vascular resistance ($p = 0.003$). These findings indicate that the expression of the PCSK enzymes is regulated by genetic factors, which have biological roles in health and disease.

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Contributors: Turpeinen, H., Seppälä, I., Lyytikäinen, L. P., Raitoharju, E., Hutri-Kähönen, N., Levula, M., Oksala, N., Waldenberger, M., Klopp, N., Illig, T., Mononen, N., Laaksonen, R., Raitakari, O., Kähönen, M., Lehtimäki, T., Pesu, M.
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**Association analysis of 9,560 prostate cancer cases from the International Consortium of Prostate Cancer Genetics confirms the role of reported prostate cancer associated SNPs for familial disease**
Previous GWAS studies have reported significant associations between various common SNPs and prostate cancer risk using cases unselected for family history. How these variants influence risk in familial prostate cancer is not well studied. Here, we analyzed 25 previously reported SNPs across 14 loci from prior prostate cancer GWAS. The International Consortium for Prostate Cancer Genetics (ICPCG) previously validated some of these using a family-based association method (FBAT). However, this approach suffered reduced power due to the conditional statistics implemented in FBAT. Here, we use a case-control design with an empirical analysis strategy to analyze the ICPCG resource for association between these 25 SNPs and familial prostate cancer risk. Fourteen sites contributed 12,506 samples (9,560 prostate cancer cases, 3,368 with aggressive disease, and 2,946 controls from 2,283 pedigrees). We performed association analysis with Genie software which accounts for relationships. We analyzed all familial prostate cancer cases and the subset of aggressive cases. For the familial prostate cancer phenotype, 20 of the 25 SNPs were at least nominally associated with prostate cancer and 16 remained significant after multiple testing correction ($p \leq 1E^{-3}$) occurring on chromosomal bands 6q25, 7p15, 8q24, 10q11, 11q13, 17q12, 17q24, and Xp11. For aggressive disease, 16 of the SNPs had at least nominal evidence and 8 were statistically significant including 2p15. The results indicate that the majority of common, low-risk alleles identified in GWAS studies for all prostate cancer also contribute risk for familial prostate cancer, and that some may contribute risk to aggressive disease.

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Contributors: Teerlink, C. C., Thibodeau, S. N., McDonnell, S. K., Schaid, D. J., Rinckleb, A., Maier, C., Vogel, W., Cancel-Tassin, G., Egrot, C., Cussenot, O., Foulkes, W. D., Giles, G. G., Hopper, J. L., Severi, G., Eeles, R., Easton, D., Kote-Jarai, Z., Guy, M., Cooney, K. A., Ray, A. M., Zuhlke, K. A., Lange, E. M., Fitzgerald, L. M., Stanford, J. L., Ostrander, E. A., Wiley, K. E., Isaacs, S. D., Walsh, P. C., Isaacs, W. B., Wahlfors, T., Tammela, T., Schleutker, J., Wiklund, F., Grönberg, H., Emanuelsson, M., Carpten, J., Bailey-Wilson, J., Whittemore, A. S., Oakley-Girvan, I., Hsieh, C. L., Catalona, W. J., Zheng, S. L., Jin, G., Lu, L., Xu, J., Camp, N. J., Cannon-Albright, L. A.
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### A Novel MMP12 Locus Is Associated with Large Artery Atherosclerotic Stroke Using a Genome-Wide Age-at-Onset Informed Approach

Genome-wide association studies (GWAS) have begun to identify the common genetic component to ischaemic stroke (IS). However, IS has considerable phenotypic heterogeneity. Where clinical covariates explain a large fraction of disease risk, covariate informed designs can increase power to detect associations. As prevalence rates in IS are markedly affected by age, and younger onset cases may have higher genetic predisposition, we investigated whether an age-at-onset informed approach could detect novel associations with IS and its subtypes; cardioembolic (CE), large artery atherosclerosis (LAA) and small vessel disease (SVD) in 6,778 cases of European ancestry and 12,095 ancestry-matched controls. Regression analysis to identify SNP associations was performed on posterior liabilities after conditioning on age-at-onset and affection status. We sought further evidence of an association with LAA in 1,881 cases and 50,817 controls, and examined mRNA expression levels of the nearby genes in atherosclerotic carotid artery plaques. Secondly, we performed permutation analyses to evaluate the extent to which age-at-onset informed analysis improves significance for novel loci. We identified a novel association with an MMP12 locus in LAA (rs660599; $p = 2.5\times10^{-7}$), with independent replication in a second population ($p = 0.0048$, OR(95% CI) = 1.18(1.05-1.32); meta-analysis $p = 2.6\times10^{-8}$). The nearby gene, MMP12, was significantly overexpressed in carotid plaques compared to atherosclerosis-free control arteries ($p = 1.2\times10^{-15}$; fold change = 335.6). Permutation analyses demonstrated improved significance for associations when accounting for age-at-onset in all four stroke phenotypes (p

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Contributors: Traylor, M., Mäkelä, K. M., Kilarski, L. L., Holliday, E. G., Devan, W. J., Nalls, M. A., Wiggins, K. L., Zhao, W. , Cheng, Y. C., Achterberg, S., Malik, R., Sudlow, C., Bevan, S., Raitoharju, E., Oksala, N., Thijs, V., Lemmens, R., Lindgren, A., Slowik, A., Maguire, J. M., Walters, M., Algra, A., Sharma, P., Attia, J. R., Boncoraglio, G. B., Rothwell, P. M. , de Bakker, P. I. W., Bis, J. C., Saleheen, D., Kittner, S. J., Mitchell, B. D., Rosand, J., Meschia, J. F., Levi, C., Dichgans, M., Lehtimäki, T., Lewis, C. M., Markus, H. S.
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### Enhancing our understanding of ways to analyze metagenomes

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Contributors: Emmert-Streib, F.
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### Relevance of different prior knowledge sources for inferring gene interaction networks
When inferring networks from high-throughput genomic data, one of the main challenges is the subsequent validation of these networks. In the best case scenario, the true network is partially known from previous research results published in structured databases or research articles. Traditionally, inferred networks are validated against these known interactions. Whenever the recovery rate is gauged to be high enough, subsequent high scoring but unknown inferred interactions are deemed good candidates for further experimental validation. Therefore such validation framework strongly depends on the quantity and quality of published interactions and presents serious pitfalls: (1) availability of these known interactions for the studied problem might be sparse; (2) quantitatively comparing different inference algorithms is not trivial; and (3) the use of these known interactions for validation prevents their integration in the inference procedure. The latter is particularly relevant as it has recently been showed that integration of priors during network inference significantly improves the quality of inferred networks. To overcome these problems when validating inferred networks, we recently proposed a data-driven validation framework based on single gene knock-down experiments. Using this framework, we were able to demonstrate the benefits of integrating prior knowledge and expression data. In this paper we used this framework to assess the quality of different sources of prior knowledge on their own and in combination with different genomic data sets in colorectal cancer. We observed that most prior sources lead to significant F -scores. Furthermore, their integration with genomic data leads to a significant increase in F -scores, especially for priors extracted from full text PubMed articles, known co-expression modules and genetic interactions. Lastly, we observed that the results are consistent for three different data sets: experimental knock-down data and two human tumor data sets.

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**The gene regulatory network for breast cancer: Integrated regulatory landscape of cancer hallmarks**

In this study, we infer the breast cancer gene regulatory network from gene expression data. This network is obtained from the application of the BC3Net inference algorithm to a large-scale gene expression data set consisting of 351 patient samples. In order to elucidate the functional relevance of the inferred network, we are performing a Gene Ontology (GO) analysis for its structural components. Our analysis reveals that most significant GO-terms we find for the breast cancer network represent functional modules of biological processes that are described by known cancer hallmarks, including translation, immune response, cell cycle, organelle fission, mitosis, cell adhesion, RNA processing, RNA splicing and response to wounding. Furthermore, by using a curated list of census cancer genes, we find an enrichment in these functional modules. Finally, we study cooperative effects of chromosomes based on information of interacting genes in the beast cancer network. We find that chromosome 21 is most coactive with other chromosomes. To our knowledge this is the first study investigating the genome-scale breast cancer network.

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Contributors: Emmert-Streib, F., Simoes, R. D. M., Mullan, P., Haibe-Kains, B., Dehmer, M.
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**Untangling statistical and biological models to understand network inference: The need for a genomics network ontology**

In this paper, we shed light on approaches that are currently used to infer networks from gene expression data with respect to their biological meaning. As we will show, the biological interpretation of these networks depends on the chosen theoretical perspective. For this reason, we distinguish a statistical perspective from a mathematical modeling perspective and elaborate their differences and implications. Our results indicate the imperative need for a genomic network ontology

in order to avoid increasing confusion about the biological interpretation of inferred networks, which can be even enhanced by approaches that integrate multiple data sets, respectively, data types.

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## Association of neuroimmune guidance cue netrin-1 and its chemorepulsive receptor UNC5B with atherosclerotic plaque expression signatures and stability in human(s) Tampere Vascular Study (TVS)

Background-Macrophage (MF) infiltration and smooth muscle cell (SMC) proliferation are hallmarks of atherosclerosis and unstable plaques. Neuroimmune guidance cue 1 (netrin-1 [NTN1]) plays a critical role controlling MF trafficking and SMC activation. Characterization of expression of NTN1 and its receptors and their association with plaque stability in human(s) is lacking. Methods and Results-The expression of NTN1 and its receptors did not differ in either whole blood or circulating monocytes from patients with coronary artery disease (n=55) compared with healthy controls (n=45). However, NTN1 was downregulated (-2.9-fold; P

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Contributors: Oksala, N., Pärssinen, J., Seppälä, I., Raitoharju, E., Ivana, K., Hernesniemi, J., Lyytikäinen, L. P., Levula, M., Mäkelä, K. M., Sioris, T., Kähönen, M., Laaksonen, R., Hytönen, V., Lehtimäki, T.
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### Genome-wide association study identifies 3 genomic loci significantly associated with serum levels of homoarginine: The atheroremo consortium

Background-Low serum levels of the amino acid derivative, homoarginine, have been associated with increased risk of total and cardiovascular mortality. Homoarginine deficiency may be related to renal and heart diseases, but the pathophysiologic role of homoarginine and the genetic regulation of its serum levels are largely unknown. Methods and Results-In 3041 patients of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study referred for coronary angiography and 2102 participants of the Young Finns Study (YFS), we performed a genome-wide association study to identify genomic loci associated with homoarginine serum levels and tested for associations of identified singlenucleotide polymorphisms with mortality in LURIC. We found genome-wide significant associations with homoarginine serum levels on chromosome 2 at the carbamoyl phosphate synthetase I locus, on chromosome 5 at the alanine-glyoxylate aminotransferase 2 locus, and on chromosome 15 at the glycine amidinotransferase locus, as well as a suggestive association on chromosome 6 at the Homo sapiens mediator complex subunit 23 gene/arginase I locus. All loci harbor enzymes located in the mitochondrium are involved in arginine metabolism. The strongest association was observed for rs1153858 at the glycine amidinotransferase locus with a P value of 1.25E-45 in the combined analysis and has been replicated in both the Die Deutsche Diabetes Dialyse Studie (4D study) and the Graz Endocrine Causes of Hypertension (GECOH) study. Conclusions-In our genome-wide association study, we identified 3 chromosomal regions significantly associated with serum homoarginine and another region with suggestive association, providing novel insights into the genetic regulation of homoarginine.

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### Somatic alterations contributing to metastasis of a castration-resistant prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) is a lethal disease, and molecular markers that differentiate indolent from aggressive subtypes are needed. We sequenced the exomes of five metastatic tumors and healthy kidney tissue from an index case with mCRPC to identify lesions associated with disease progression and metastasis. An Ashkenazi Jewish (AJ) germline founder mutation, del185AG in BRCA1, was observed and AJ ancestry was confirmed.

Sixty-two somatic variants altered proteins in tumors, including cancer-associated genes, TMPRSS2-ERG, PBRM1, and TET2. The majority (n = 53) of somatic variants were present in all metastases and only a subset (n = 31) was observed in the primary tumor. Integrating tumor next-generation sequencing and DNA copy number showed somatic loss of BRCA1 and TMPRSS2-ERG. We sequenced 19 genes with deleterious mutations in the index case in additional mCRPC samples and detected a frameshift, two somatic missense alterations, tumor loss of heterozygosity, and combinations of germline missense SNPs in TET2. In summary, genetic analysis of metastases from an index case permitted us to infer a chronology for the clonal spread of disease based on sequential accrual of somatic lesions. The role of TET2 in mCRPC deserves additional analysis and may define a subset of metastatic disease.

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Contributors: Nickerson, M. L., Im, K. M., Misner, K. J., Tan, W., Lou, H., Gold, B., Wells, D. W., Bravo, H. C., Fredrikson, K. M., Harkins, T. T., Milos, P., Zbar, B., Linehan, W. M., Yeager, M., Andresson, T., Dean, M., Bova, G. S.
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## Genetic heterogeneity in Finnish hereditary prostate cancer using ordered subset analysis

Prostate cancer (PrCa) is the most common male cancer in developed countries and the second most common cause of cancer death after lung cancer. We recently reported a genome-wide linkage scan in 69 Finnish hereditary PrCa (HPC) families, which replicated the HPC9 locus on 17q21-q22 and identified a locus on 2q37. The aim of this study was to identify and to detect other loci linked to HPC. Here we used ordered subset analysis (OSA), conditioned on nonparametric linkage to these loci to detect other loci linked to HPC in subsets of families, but not the overall sample. We analyzed the families based on their evidence for linkage to chromosome 2, chromosome 17 and a maximum score using the strongest evidence of linkage from either of the two loci. Significant linkage to a 5-cM linkage interval with a peak OSA nonparametric allele-sharing LOD score of 4.876 on Xq26.3-q27 (ΔLOD=3.193, empirical P=0.009) was observed in a subset of 41 families weakly linked to 2q37, overlapping the HPCX1 locus. Two peaks that were novel to the analysis combining linkage evidence from both primary loci were identified; 18q12.1-q12.2 (OSA LOD=2.541, ΔLOD=1.651, P=0.03) and 22q11.1-q11.21 (OSA LOD=2.395, ΔLOD=2.36, P=0.006), which is close to HPC6. Using OSA allows us to find additional loci linked to HPC in subsets of families, and underlines the complex genetic heterogeneity of HPC even in highly aggregated families.

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Contributors: Simpson, C. L., Cropp, C. D., Wahlfors, T., George, A., Jones, M. S., Harper, U., Ponciano-Jackson, D., Tammela, T., Schleutker, J., Bailey-Wilson, J. E.
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**A meta-analysis of genome-wide association studies to identify prostate cancer susceptibility loci associated with aggressive and non-aggressive disease**

Genome-wide association studies (GWAS) have identified multiple common genetic variants associated with an increased risk of prostate cancer (PrCa), but these explain less than one-third of the heritability. To identify further susceptibility alleles, we conducted a meta-analysis of four GWAS including 5953 cases of aggressive PrCa and 11 463 controls (men without PrCa). We computed association tests for approximately 2.6 million SNPs and followed up the most significantSNPs by genotyping 49 121 samples in 29 studies through the international PRACTICAL and BPC3 consortia. We not only confirmed the association of a PrCa susceptibility locus, rs11672691 on chromosome 19, but also showed an association with aggressive PrCa [odds ratio = 1.12 (95% confidence interval 1.03-1.21), $P = 1.4 \times 10^{-8}$]. This report describes a genetic variant which is associated with aggressive PrCa, which is a type of PrCa associated with a poorer prognosis.

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Contributors: Al Olama, A. A., Kote-Jarai, Z., Schumacher, F. R., Wiklund, F., Berndt, S. I., Benlloch, S., Giles, G. G., Severi, G., Neal, D. E., Hamdy, F. C., Donovan, J. L., Hunter, D. J., Henderson, B. E., Thun, M. J., Gaziano, M., Giovannucci, E. L., Siddiq, A., Travis, R. C., Cox, D. G., Canzian, F., Riboli, E., Key, T. J., Andriole, G., Albanes, D., Hayes, R. B., Schleutker, J., Auvinen, A., Tammela, T. L. J., Weischer, M., Stanford, J. L., Ostrander, E. A., Cybulski, C., Lubinski, J., Thibodeau, S. N., Schaid, D. J., Sorensen, K. D., Batra, J., Clements, J. A., Chambers, S., Aitken, J., Gardiner, R. A., Maier, C., Vogel, W., Dörk, T., Brenner, H., Habuchi, T., Ingles, S., John, E. M., Dickinson, J. L., Cannon-Albright, L., Teixeira, M. R., Kaneva, R., Zhang, H. W., Lu, Y. J., Park, J. Y., Cooney, K. A., Muir, K. R., Leongamornlert, D. A., Saunders, E., Tymrakiewicz, M., Mahmud, N., Guy, M., Govindasami, K., O'Brien, L. T., Wilkinson, R. A., Hall, A. L. , Sawyer, E. J., Dadaev, T., Morrison, J., Dearnaley, D. P., Horwich, A., Huddart, R. A., Khoo, V. S., Parker, C. C., Van As, N., Woodhouse, C. J., Thompson, A., Dudderidge, T., Ogden, C., Cooper, C. S., Lophatonanon, A., Southey, M. C., Hopper, J. L., English, D., Virtamo, J., Marchand, L. L., Campa, D., Kaaks, R., Lindstrom, S., Diver, W. R., Gapstur, S.,

Yeager, M., Cox, A., Stern, M. C., Corral, R., Aly, M., Isaacs, W., Adolfsson, J., Xu, J., Zheng, S. L., Wahlfors, T., Taari, K. , Kujala, P., Klarskov, P., Nordestgaard, B. G., Røder, M. A., Frikke-Schmidt, R., Bojesen, S. E., FitzGerald, L. M., Kolb, S. , Kwon, E. M., Karyadi, D. M., Orntoft, T. F., Borre, M., Rinckleb, A., Luedeke, M., Herkommer, K., Meyer, A., Serth, J. R., Marthick, J. R., Patterson, B., Wokolorczyk, D., Spurdle, A., Lose, F., McDonnell, S. K., Joshi, A. D., Shahabi, A., Pinto, P. , Santos, J., Ray, A., Sellers, T. A., Lin, H. Y., Stephenson, R. A., Teerlink, C., Muller, H., Rothenbacher, D., Tsuchiya, N., Narita, S., Cao, G. W., Slavov, C., Mitev, V., Chanock, S., Gronberg, H., Haiman, C. A., Kraft, P., Easton, D. F., Eeles, R. A.
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### HOXB13 is a susceptibility gene for prostate cancer: Results from the International Consortium for Prostate Cancer Genetics (ICPCG)

Prostate cancer has a strong familial component but uncovering the molecular basis for inherited susceptibility for this disease has been challenging. Recently, a rare, recurrent mutation (G84E) in HOXB13 was reported to be associated with prostate cancer risk. Confirmation and characterization of this finding is necessary to potentially translate this information to the clinic. To examine this finding in a large international sample of prostate cancer families, we genotyped this mutation and 14 other SNPs in or flanking HOXB13 in 2,443 prostate cancer families recruited by the International Consortium for Prostate Cancer Genetics (ICPCG). At least one mutation carrier was found in 112 prostate cancer families (4.6 %), all of European descent. Within carrier families, the G84E mutation was more common in men with a diagnosis of prostate cancer (194 of 382, 51 %) than those without (42 of 137, 30 %), $P = 9.9 \times 10^{-8}$ [odds ratio 4.42 (95 % confidence interval 2.56-7.64)]. A family-based association test found G84E to be significantly over-transmitted from parents to affected offspring ($P = 6.5 \times 10^{-6}$). Analysis of markers flanking the G84E mutation indicates that it resides in the same haplotype in 95 % of carriers, consistent with a founder effect. Clinical characteristics of cancers in mutation carriers included features of high-risk disease. These findings demonstrate that the HOXB13 G84E mutation is present in ~5 % of prostate cancer families, predominantly of European descent, and confirm its association with prostate cancer risk. While future studies are needed to more fully define the clinical utility of this observation, this allele and others like it could form the basis for early, targeted screening of men at elevated risk for this common, clinically heterogeneous cancer.

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Contributors: Xu, J., Lange, E. M., Lu, L., Zheng, S. L., Wang, Z., Thibodeau, S. N., Cannon-Albright, L. A., Teerlink, C. C. , Camp, N. J., Johnson, A. M., Zuhlke, K. A., Stanford, J. L., Ostrander, E. A., Wiley, K. E., Isaacs, S. D., Walsh, P. C., Maier, C., Luedeke, M., Vogel, W., Schleutker, J., Wahlfors, T., Tammela, T., Schaid, D., McDonnell, S. K., Derycke, M. S. , Cancel-Tassin, G., Cussenot, O., Wiklund, F., Grönberg, H., Eeles, R., Easton, D., Kote-Jarai, Z., Whittemore, A. S., Hsieh, C. L., Giles, G. G., Hopper, J. L., Severi, G., Catalona, W. J., Mandal, D., Ledet, E., Foulkes, W. D., Hamel, N., Mahle, L., Moller, P., Powell, I., Bailey-Wilson, J. E., Carpten, J. D., Seminara, D., Cooney, K. A., Isaacs, W. B.

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**B-cell lymphoma gene regulatory networks: Biological consistency among inference methods**
Despite the development of numerous gene regulatory network (GRN) inference methods in the last years, their application, usage and the biological significance of the resulting GRN remains unclear for our general understanding of large-scale gene expression data in routine practice. In our study, we conduct a structural and a functional analysis of B-cell lymphoma GRNs that were inferred using 3 mutual information-based GRN inference methods: $C_3$Net, $BC_3$Net and Aracne. From a comparative analysis on the global level, we find that the inferred B-cell lymphoma GRNs show major differences. However, on the edge-level and the functional-level-that are more important for our biological understanding-the B-cell lymphoma GRNs were highly similar among each other. Also, the ranks of the degree centrality values and major hub genes in the inferred networks are highly conserved as well. Interestingly, the major hub genes of all GRNs are associated with the G-protein-coupled receptor pathway, cell-cell signaling and cell cycle. This implies that hub genes of the GRNs can be highly consistently inferred with $C_3$Net, $BC_3$Net, and Aracne, representing prominent targets for signaling pathways. Finally, we describe the functional and structural relationship between $C_3$Net, $BC_3$Net and Aracne gene regulatory networks. Our study shows that these GRNs that are inferred from large-scale gene expression data are promising for the identification of novel candidate interactions and pathways that play a key role in the underlying mechanisms driving cancer hallmarks. Overall, our comparative analysis reveals that these GRNs inferred with considerably different inference methods contain large amounts of consistent, method independent, biological information.

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### Personalized medicine: Has it started yet? A reconstruction of the early history

Within the last few years the field personalized medicine entered the stage. Accompanied with great hopes and expectations it is believed that this field may have the potential to revolutionize medical and clinical care by utilizing genomics information about the individual patients themselves. In this paper, we reconstruct the early footprints of personalized medicine as reflected by information retrieved from PubMed and Google Scholar. That means we are providing a data-driven perspective of this field to estimate its current status and potential problems.

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Contributors: Emmert-Streib, F.
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### Loss of SUFU function in familial multiple meningioma

Meningiomas are the most common primary tumors of the CNS and account for up to 30% of all CNS tumors. An increased risk of meningiomas has been associated with certain tumor-susceptibility syndromes, especially neurofibromatosis type II, but no gene defects predisposing to isolated familial meningiomas have thus far been identified. Here, we report on a family of five meningioma-affected siblings, four of whom have multiple tumors. No NF2 mutations were identified in the germline or tumors. We combined genome-wide linkage analysis and exome sequencing, and we identified in suppressor of fused homolog (Drosophila), SUFU, a c.367C>T (p.Arg123Cys) mutation segregating with the meningiomas in the family. The variation was not present in healthy controls, and all seven meningiomas analyzed displayed loss of the wild-type allele according to the classic two-hit model for tumor-suppressor genes. In silico modeling predicted the variant to affect the tertiary structure of the protein, and functional analyses showed that the activity of the altered SUFU was significantly reduced and therefore led to dysregulated hedgehog (Hh) signaling. SUFU is a known tumor-suppressor gene previously associated with childhood medulloblastoma predisposition. Our genetic and functional analyses indicate that germline mutations in SUFU also predispose to meningiomas, particularly to multiple meningiomas. It is possible that other genic mutations resulting in aberrant activation of the Hh pathway might underlie meningioma predisposition in families with an unknown etiology.

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Contributors: Aavikko, M., Li, S. P., Saarinen, S., Alhopuro, P., Kaasinen, E., Morgunova, E., Li, Y., Vesanen, K., Smith, M. J., Evans, D. G. R., Pöyhönen, M., Kiuru, A., Auvinen, A., Aaltonen, L. A., Taipale, J., Vahteristo, P.
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**Novel Loci for Metabolic Networks and Multi-Tissue Expression Studies Reveal Genes for Atherosclerosis**
Association testing of multiple correlated phenotypes offers better power than univariate analysis of single traits. We analyzed 6,600 individuals from two population-based cohorts with both genome-wide SNP data and serum metabolomic profiles. From the observed correlation structure of 130 metabolites measured by nuclear magnetic resonance, we identified 11 metabolic networks and performed a multivariate genome-wide association analysis. We identified 34 genomic loci at genome-wide significance, of which 7 are novel. In comparison to univariate tests, multivariate association analysis identified nearly twice as many significant associations in total. Multi-tissue gene expression studies identified variants in our top loci, SERPINA1 and AQP9, as eQTLs and showed that SERPINA1 and AQP9 expression in human blood was associated with metabolites from their corresponding metabolic networks. Finally, liver expression of AQP9 was associated with atherosclerotic lesion area in mice, and in human arterial tissue both SERPINA1 and AQP9 were shown to be upregulated (6.3-fold and 4.6-fold, respectively) in atherosclerotic plaques. Our study illustrates the power of multi-phenotype GWAS and highlights candidate genes for atherosclerosis.

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Contributors: Inouye, M., Ripatti, S., Kettunen, J., Lyytikäinen, L. P., Oksala, N., Laurila, P. P., Kangas, A. J., Soininen, P., Savolainen, M. J., Viikari, J., Kähönen, M., Perola, M., Salomaa, V., Raitakari, O., Lehtimäki, T., Taskinen, M. R., Järvelin, M. R., Ala-Korpela, M., Palotie, A., de Bakker, P. I. W.
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## Validation of prostate cancer risk-related loci identified from genome-wide association studies using family-based association analysis: Evidence from the International Consortium for Prostate Cancer Genetics (ICPCG)

Multiple prostate cancer (PCa) risk-related loci have been discovered by genome-wide association studies (GWAS) based on case-control designs. However, GWAS findings may be confounded by population stratification if cases and controls are inadvertently drawn from different genetic backgrounds. In addition, since these loci were identified in cases with predominantly sporadic disease, little is known about their relationships with hereditary prostate cancer (HPC). The association between seventeen reported PCa susceptibility loci was evaluated with a family-based association test using 1,979 hereditary PCa families of European descent collected by members of the International Consortium for Prostate Cancer Genetics, with a total of 5,730 affected men. The risk alleles for 8 of the 17 loci were significantly over-transmitted from parents to affected offspring, including SNPs residing in 8q24 (regions 1, 2 and 3), 10q11, 11q13, 17q12 (region 1), 17q24 and Xp11. In subgroup analyses, three loci, at 8q24 (regions 1 and 2) plus 17q12, were significantly over-transmitted in hereditary PCa families with five or more affected members, while loci at 3p12, 8q24 (region 2), 11q13, 17q12 (region 1), 17q24 and Xp11 were significantly over-transmitted in HPC families with an average age of diagnosis at 65 years or less. Our results indicate that at least a subset of PCa risk-related loci identified by case-control GWAS are also associated with disease risk in HPC families.

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Contributors: Jin, G., Lu, L., Cooney, K. A., Ray, A. M., Zuhlke, K. A., Lange, E. M., Cannon-Albright, L. A., Camp, N. J., Teerlink, C. C., Fitzgerald, L. M., Stanford, J. L., Wiley, K. E., Isaacs, S. D., Walsh, P. C., Foulkes, W. D., Giles, G. G., Hopper, J. L., Severi, G., Eeles, R., Easton, D., Kote-Jarai, Z., Guy, M., Rinckleb, A., Maier, C., Vogel, W., Cancel-Tassin, G., Egrot, C., Cussenot, O., Thibodeau, S. N., McDonnell, S. K., Schaid, D. J., Wiklund, F., Grönberg, H., Emanuelsson, M., Whittemore, A. S., Oakley-Girvan, I., Hsieh, C. L., Wahlfors, T., Tammela, T., Schleutker, J., Catalona, W. J., Zheng, S. L., Ostrander, E. A., Isaacs, W. B., Xu, J.
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## Analysis of Xq27-28 linkage in the international consortium for prostate cancer genetics (ICPCG) families

Background: Genetic variants are likely to contribute to a portion of prostate cancer risk. Full elucidation of the genetic etiology of prostate cancer is difficult because of incomplete penetrance and genetic and phenotypic heterogeneity. Current evidence suggests that genetic linkage to prostate cancer has been found on several chromosomes including the X; however, identification of causative genes has been elusive.Methods: Parametric and non-parametric linkage analyses were performed using 26 microsatellite markers in each of 11 groups of multiple-case prostate cancer families from the International Consortium for Prostate Cancer Genetics (ICPCG). Meta-analyses of the resultant family-specific linkage statistics across the entire 1,323 families and in several predefined subsets were then performed.Results: Meta-analyses of linkage statistics resulted in a maximum parametric heterogeneity lod score (HLOD) of 1.28, and an allele-sharing lod score (LOD) of 2.0 in favor of linkage to Xq27-q28 at 138 cM. In subset analyses, families with average age at onset less than 65 years exhibited a maximum HLOD of 1.8 (at 138 cM) versus a maximum regional HLOD of only 0.32 in families with average age at onset of 65 years or older. Surprisingly, the subset of families with only 2-3 affected men and some

evidence of male-to-male transmission of prostate cancer gave the strongest evidence of linkage to the region (HLOD = 3.24, 134 cM). For this subset, the HLOD was slightly increased (HLOD = 3.47 at 134 cM) when families used in the original published report of linkage to Xq27-28 were excluded.Conclusions: Although there was not strong support for linkage to the Xq27-28 region in the complete set of families, the subset of families with earlier age at onset exhibited more evidence of linkage than families with later onset of disease. A subset of families with 2-3 affected individuals and with some evidence of male to male disease transmission showed stronger linkage signals. Our results suggest that the genetic basis for prostate cancer in our families is much more complex than a single susceptibility locus on the X chromosome, and that future explorations of the Xq27-28 region should focus on the subset of families identified here with the strongest evidence of linkage to this region.

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Contributors: Bailey-Wilson, J. E., Childs, E. J., Cropp, C. D., Schaid, D. J., Xu, J., Camp, N. J., Cannon-Albright, L. A., Farnham, J. M., George, A., Powell, I., Carpten, J. D., Giles, G. G., Hopper, J. L., Severi, G., English, D. R., Foulkes, W. D., Mæhle, L., Møller, P., Eeles, R., Easton, D., Guy, M., Edwards, S., Badzioch, M. D., Whittemore, A. S., Oakley-Girvan, I., Hsieh, C. L., Dimitrov, L., Stanford, J. L., Karyadi, D. M., Deutsch, K., McIntosh, L., Ostrander, E. A., Wiley, K. E., Isaacs, S. D., Walsh, P. C., Thibodeau, S. N., McDonnell, S. K., Hebbring, S., Lange, E. M., Cooney, K. A., Tammela, T. L. J., Schleutker, J., Maier, C., Bochum, S., Hoegel, J., Grönberg, H., Wiklund, F., Emanuelsson, M., Cancel-Tassin, G., Valeri, A., Cussenot, O., Isaacs, W. B.
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Source ID: 84862273373
Research output: Contribution to journal › Article › Scientific › peer-review

**Baculovirus-mediated vascular endothelial growth factor-DΔNΔC gene transfer induces angiogenesis in rabbit skeletal muscle**
Background: Occluded arteries and ischemic tissues cannot always be treated by angioplasty, stenting or by-pass-surgery. Under such circumstances, viral gene therapy may be useful in inducing increased blood supply to ischemic area. There is evidence of improved blood flow in ischemic skeletal muscle and myocardium in both animal and human studies using adenoviral vascular endothelial growth factor (VEGF) gene therapy. However, the expression is transient and repeated gene transfers with the same vector are inefficient due to immune responses. Methods: Different baculoviral vectors pseudotyped with or without vesicular stomatitis virus glycoprotein (VSV-G) and/or carrying woodchuck hepatitis virus post-transcriptional regulatory element (Wpre) were tested both in vitro and in vivo. VEGF-$D^{\Delta N\Delta C}$ was used as therapeutic transgene and lacZ as a control. In vivo efficacy was evaluated as capillary enlargement and transgene expression in New Zealand White (NZW) rabbit skeletal muscle. Results: A statistically significant capillary enlargement was detected 6days after gene transfer in transduced areas compared to the control gene transfers with baculovirus and adenovirus encoding β-galactosidase (lacZ). Substantially improved gene transfer efficiency was achieved with a modified baculovirus pseudotyped with VSV-G and carrying Wpre. Dose escalation experiments revealed that either too large volume or too many virus particles caused inflammation and necrosis in the target tissue, whereas $10^9$ plaque forming units injected in multiple aliquots resulted in transgene expression with only mild immune reactions. Conclusions: We show the first evidence of biologically significant baculoviral gene transfer in skeletal muscle of NZW rabbits using VEGF-$D^{\Delta N\Delta C}$ as a therapeutic transgene.

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Contributors: Heikura, T., Nieminen, T., Roschier, M. M., Karvinen, H., Kaikkonen, M. U., Mähönen, A. J., Lesch, H. P., Rissanen, T. T., Laitinen, O. H., Airenne, K. J., Ylä-Herttuala, S.
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## Statistical inference and reverse engineering of gene regulatory networks from observational expression data
In this paper, we present a systematic and conceptual overview of methods for inferring gene regulatory networks from observational gene expression data. Further, we discuss two classic approaches to infer causal structures and compare them with contemporary methods by providing a conceptual categorization thereof. We complement the above by surveying global and local evaluation measures for assessing the performance of inference algorithms.

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Contributors: Emmert-Streib, F., Glazko, G. V., Altay, G., Simoes, R. D. M.
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### Ras regulates interleukin-1β-induced HIF-1α transcriptional activity in glioblastoma

We observed elevated levels of pro-inflammatory cytokine IL-1β in glioblastoma multiforme tumor samples. Since hypoxia-inducible factor-1α (HIF-1α) plays a crucial role in linking inflammatory and oncogenic pathways, we investigated the effect of IL-1β on HIF-1α expression in glioma cells under normoxia. IL-1β-mediated elevation of HIF-1α transcriptional activity was dependent on Ras-induced NF-κB activation, as IL-1β failed to induce NF-κB and HIF-1α activity in cells transfected with dominant negative RasN17. Increased Ras expression was accompanied by increased phosphorylation of Ras effectors AKT, ERK, JNK, and p38MAPK. While inhibition of these effectors individually failed to block the IL-1β-mediated increase in HIF-1α induction, co-inhibition of both AKT and ERK resulted in a significant decrease in IL-1β-induced HIF-1α activation. Interestingly, IL-1β elevated Wnt-1 expression in a Ras-dependent manner, and small interfering RNA (siRNA)-mediated knockdown of Wnt-1 decreased HIF-1α activity. Although Wnt-1-mediated HIF-1α was independent of the canonical Wnt/β-catenin signaling pathway, it regulated HIF-1α through NF-κB. siRNA-mediated HIF-1α knockdown attenuated elevated IL-1β mRNA levels induced upon IL-1β treatment. This was accompanied by increased interaction of HIF-1α with HIF responsive element on the IL-1β promoter upon IL-1β treatment, under normoxia. Our studies highlights for first time that (1) Ras is a key mediator of IL-1β-induced NF-κB and HIF-1α activation, under normoxia; (2) Wnt-1 regulates IL-1β-mediated HIF-1α induction via NF-κB; (3) Ras and Wnt-1 are intermediaries in the canonical IL-1β-NF-κB signaling pathway downstream of MyD88; and (4) IL-1β-induced HIF-1α drives a HIF-1α-IL-1β autocrine loop to maintain persistently elevated IL-1β level.

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Contributors: Sharma, V., Dixit, D., Koul, N., Mehta, V. S., Sen, E.
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### Mutation spectra of the drinking water mutagen 3-chloro-4-methyl-5- hydroxy-2(5H)-furanone (MCF) in Salmonella TA100 and TA104: Comparison to MX

The chlorinated drinking water mutagen 3-chloro-4-methyl-5-hydroxy- 2(5H)-furanone (MCF) occurs at concentrations similar to or greater than that of the related furanone 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX). MCF and MX differ structurally only by replacement of a 3-methyl in MCF with a 3-dichloromethyl in MX; yet, MCF is significantly less mutagenic than MX and produces different adducts when reacted with nucleosides or DNA. To explore further the effects that these structural differences might have on the biological activity of MCF and MX, we determined the mutation spectra of MCF in Salmonella strains TA100 and TA 104 and of MX in strain TA104; the spectrum of MX in TA100 had been determined previously. In TA100, which presents only GC targets for mutagenesis, MCF induced primarily (75%) GC → TA transversions, with most of the remaining revertants (20%) being GC → AT transitions. This spectrum was not significantly different from that of MX in TA100 (P = 0.07). In TA104, which presents both GC and AT targets, MCF induced a lower percentage (57%) of GC → TA transversions, with most of the remaining revertants (33%) being AT → TA transversions. In contrast, MX induced almost only (98%) GC → TA transversions in TA104, with the remaining revertants (2%) being AT → TA transversions. Thus, almost all (98%) of the MX mutations were targeted at GC sites in TA104, whereas only 63% of the MCF mutations were so targeted. These results are consistent with the published findings that MX: (1) forms an adduct on guanosine when reacted with guanosine, (2) induces apurinic sites in DNA, and (3) forms a minor adduct on adenosine when reacted with adenosine or DNA. The results are also consistent with

evidence that MCF forms adenosine adducts when reacted with adenosine. Our results show that the replacement of the 4-methyl in MCF with a 4- dichloromethyl to form MX not only increases dramatically the mutagenic potency but also shifts significantly the mutagenic specificity from almost equal targeting of GC and AT sites by MCF to almost exclusive targeting of GC sites by MX.

### General information

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Contributors: Shaughnessy, D. T., Ohe, T., Landi, S., Warren, S. H., Richard, A. M., Munter, T., Franzén, R., Kronberg, L. , DeMarini, D. M.
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## Induction of genotoxic effects by chlorohydroxyfuranones, byproducts of water disinfection, in E. coli K-12 cells recovered from various organs of mice

The genotoxic effects of three chlorohydroxyfuranones (CHFs), 3-chloro-4-(dichloromethy)-5-hydroxy-2[5H]-furanone (MX), 3-chloro-4-(chloromethyl)-5-hydroxy-2[5H]furanone (CMCF) and 3,4,-dichloro-5-hydroxy-2[5H]furanone (MCA), which are formed as byproducts of water disinfection with chlorine, were investigated in bacterial differential DNA repair assays in vitro and in animal-mediated assays in vivo. As indicators of DNA damage, E. coli K-12 strains were used that differ in their repair capacity (uvrB/recA vs. uvr+/rec+). Liquid incubation of the compounds without metabolic activation caused a pronounced reduction of the viability of the repair-deficient strain relative to the repair-proficient wild-type strain. The order of potency of genotoxic activity in vitro (dose range 0.004-10 μg/ml) was MX > CMCF > MCA. Addition of mouse S-9 mix or bovine serum albumin to the incubation mixtures resulted in an almost complete loss of the activity of all three test compounds. In the animal-mediated assays, mixtures of the indicator bacteria were injected intravenously into mice which were subsequently treated with the test compounds (200 mg/kg b.w.). Two hours later, the cells were recovered from various organs and the relative survival frequencies determined. Under these conditions, all three compounds caused pronounced genotoxic effects, MX and CMCF being stronger genotoxins than MCA. The strongest effects were consistently found in the gastrointestinal tract, but statistically significant DNA damage was also observed in indicator cells recovered from lungs, liver, spleen and kidneys. In a further experiment, the effects of lower doses of MX (4.3, 13 and 40 mg/kg) were investigated. In these experiments dose-dependent effects were measured in all organs. CMCF and MA caused only marginal effects at 40 mg/kg except in the stomach where approximately a 50% reduction of relative survival frequency was observed with CMCF. The results of these animal-mediated assays indicate that (i) all three CHFs cause genotoxic effects in the living animal, and (ii) the potencies of the three compounds observed under in vivo conditions are not commensurate with their extremely high activities measured in vitro. One possible explanation for the weaker responses observed in the animal-mediated assays might be that CHFs ore inactivated by nonspecific protein binding.

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10.1002/em.2850240409
URLs:
http://www.scopus.com/inward/record.url?scp=0028618759&partnerID=8YFLogxK (Link to publication in Scopus)
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