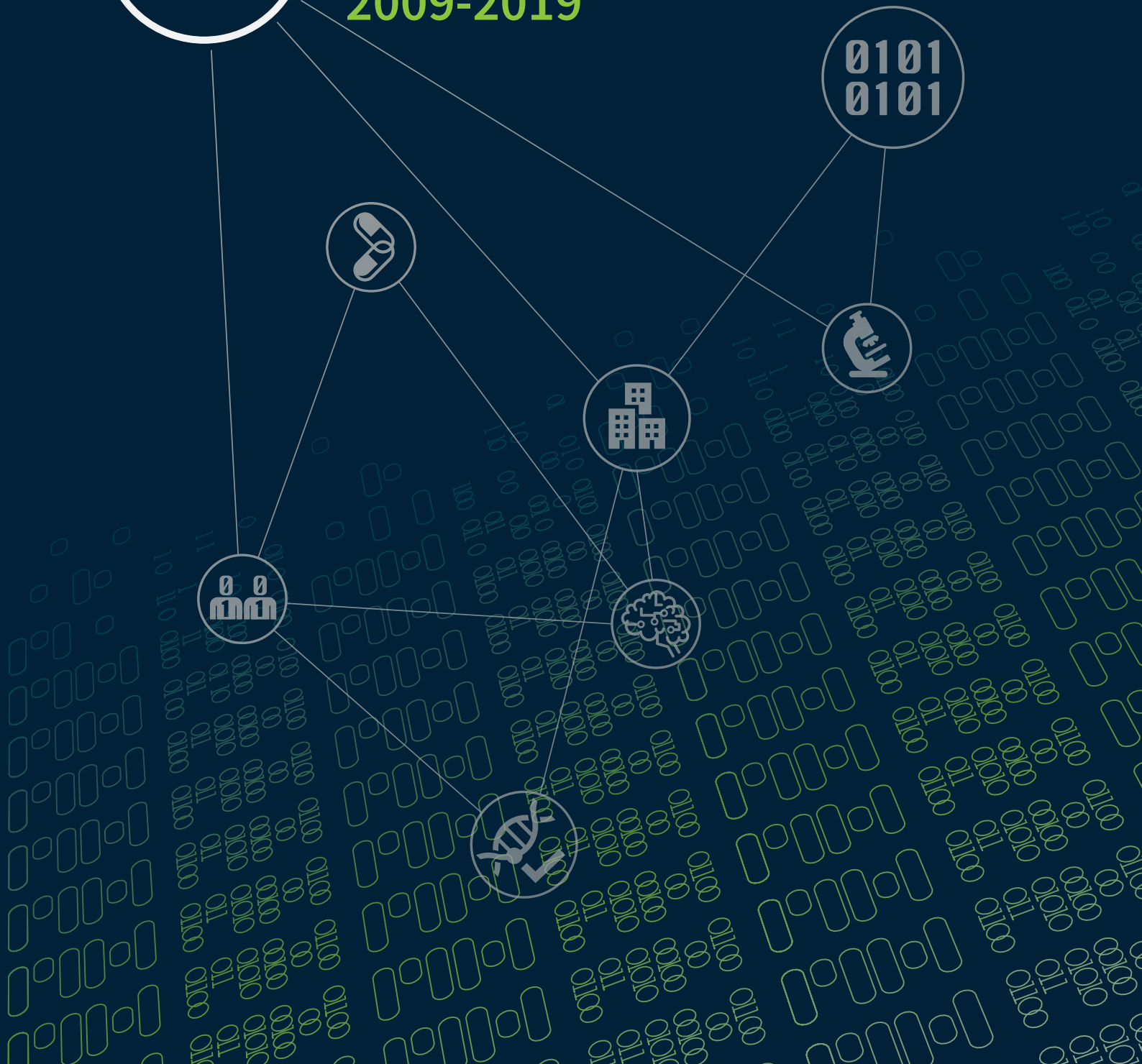
MOLECULAR HEALTH

Catalogue of peer-reviewed studies 2009-2019



Content

Highlights

Src activation by β-adrenoreceptors is a key switch for tumour metastasis. 4

Erythropoietin stimulates tumor growth via ephB4. 5

Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer. 6

Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities. 7

Abstracts

1. Clinical and economic impact of the non-responder phenomenon-implications for systems based discovery. 8
2. Molecular perspectives on the non-responder phenomenon. 8
3. Serum-based microRNAs: are we blinded by potential? 9
4. Drug profiling: knowing where it hits. 9
5. LAITOR - Literature assistant for identification of terms co-occurrences and relationships. 10
6. EMT is the dominant program in human colon cancer. 10
7. Genetic determinants of anticancer drug activity: towards a global approach to personalized cancer medicine. 11
8. Intelligent clinical decision support systems for non-invasive bladder cancer diagnosis. 11
9. Personalized cancer medicine-advances and socio-economic challenges. 12
10. Using graph theory to analyze biological networks. 12
11. A scatter-based prototype framework and multi-class extension of support vector machines. 13
12. Biggest challenges in bioinformatics. 13
13. Systemic microRNA measurement, a useful tool for predicting diagnosis in bladder cancer. 14
14. Src activation by β-adrenoreceptors is a key switch for tumour metastasis. 14
15. Drugs highly associated with Infusion reactions reported using two different data-mining methodologies. 15
16. Data mining FAERS to analyse molecular targets highly associated with Stevens Johnson Syndrome. 15
17. How to learn about gene function: text-mining or ontologies? 16
18. Relationships of clinical response to relevant molecular signal during Phase I testing of Aurora Kinase a inhibitor: Retrospective assessment. 16
19. Erythropoietin Stimulates Tumor Growth via EphB4. 17
20. Improving drug safety with a systems pharmacology approach. 17
21. Use of “big data” in drug discovery and clinical trials. 18
22. A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC. 18
23. Reliability of algorithmic somatic copy number alteration detection from targeted capture data. 19
24. Comprehensive benchmarking of SNV callers for highly admixed tumors. 19
25. Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer. 20
26. Association between serotonin syndrome and second-generation antipsychotics via pharmacological target-adverse event analysis. 20
27. In silico profiling of clinical phenotypes for human targets using adverse event data. 21
28. A neural autoencoder approach for document ranking and query refinement in pharmacogenomic information retrieval. 21
29. Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities. 22
30. Adverse event circumstances and the case of drug interactions. 22
31. Precision Oncology - The quest for evidence. 23
32. Radioimmunotherapy in non-Hodgkin’s Lymphoma: Retrospective adverse event profiling of zevalin and bexxar. 23

Peer-reviewed studies 2009-2019

Over the past decade, Molecular Health has forged an open innovation policy that has led to successful collaborations with some of the worlds most renowned biomedical institutes and innovators. Together, we focused on some of the most important challenges in healthcare with Molecular Health providing the backbone of clinico-molecular data and cutting-edge analytical strategies.

These diverse endeavors included issues such as improving the detection and prediction of safety concerns for new and approved drugs, to the application of genome guided treatment decision support across cancer patients in clinical trial contexts. This work has not only lead to the development of novel computational approaches to issues such as drug repositioning, or rationale design of drug combinations, but also to the discovery of novel predictive biomarkers.

While much of this work has been presented at globally renowned conferences (e.g. ASCO, AACR, ESMO, ACMG, PMWC and Bio-IT), here we detail peer-reviewed submissions, successfully published in journals such as Cancer Cell, Proceedings of the National Academy of Sciences, Nature Communications and Nature reviews in Clinical Oncology. For each paper, we not only provide the abstract and reference, but also detail the specific collaboration partner (if involved) and the MH analytical technology used.

About Molecular Health

Molecular Health is a transformational biomedical intelligence company, improving human health by liberating the power of clinical and molecular data. Capitalizing on our Dataome technology platform, we perpetually capture, enrich and integrate the world´s biomedical data in a quality-controlled environment – delivering more intelligible data for healthcare.

We utilize this evidence base to build disruptive analytical technologies that enable knowledge creation and paradigm change throughout the healthcare ecosystem. These are the innovations that empower our customers to deliver better treatments, diagnoses and disease prevention.

Highlight

Novel approach to drug repositioning/ combination therapy design

Src activation by β-adrenoreceptors is a key switch for tumour metastasis.

What was the current knowledge on the topic prior to this work?
Clinical and animal studies support the notion that psychological factors such as stress, chronic depression, and lack of social support might promote tumor growth and progression. The molecular mechanisms responsible for these effects were up to this time largely unknown.

What question did this study address?
Previous work determined that sympathetic nervous system activity can directly enhance the pathogenesis of ovarian carcinoma by protecting tumor cells from anoikis, promoting tumor cell invasion and tumor-associated angiogenesis. We found that these effects were mediated through activation of tumor cell ADRB2 (Adrenergic Receptor), but its downstream signaling pathways were not well understood. This study sought to characterize these mechanisms.

What did this study add to our knowledge?
In this study, we used the Dataome Knowledgebase to predict a signalling network downstream of ADRB. Subsequent laboratory -ased validation demonstrated that ADRB signaling leads to Src activation by a unique PKA-mediated mechanism, which is critical to the regulation of phosphoproteomic networks associated with ovarian cancer progression.

How might this change drug discovery, development, and/or therapeutics?
On the basis of our work, beta-antagonists were shown to abrogate many of the deleterious effects of increased adrenergic signaling in response to bio-behavioral stress. The findings supported the use of Src family kinase inhibitors as tools to block the deleterious effects of increased sympathetic activity. Collectively, the data represented a new understanding of Src regulation in response to adrenergic signaling in cancer cells and provided a biologically plausible and potent way of inhibiting tumor progression among cancer patients.

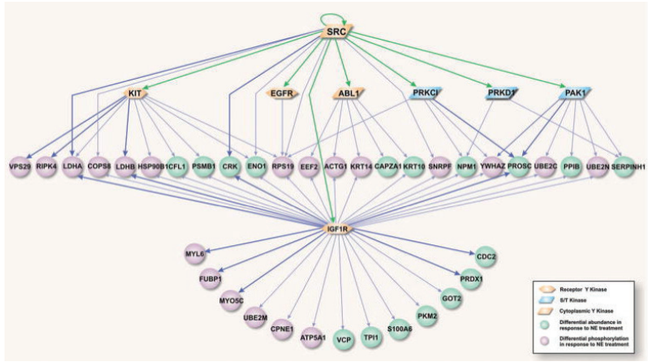


Figure Legend. Putative phosphorylation cascade triggered by the NE-induced activation of Src

Here we used the Dataome Knowledgebase to predict a signalling network downstream of SRC in response to ADRB2 activation by Norepinephrine (NE).

For more information, see abstract number 14.

Journal

nature COMMUNICATIONS

Reference

Nat Commun. 2013;4:1403. PMID: 23360994

2013

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH EFFECT

Highlight

Discovery of a novel predictive biomarker

Erythropoietin stimulates tumor growth via ephB4.

What was the current knowledge on the topic prior to this work?
Recombinant human Erythropoietin (rhEpo) was commonly prescribed to treat chemotherapy induced anemia in cancer patients. Many retrospective studies suggested poorer overall survival and progression free survival in response to rhEpo treatment. Available evidence suggested that the EPO receptor was not responsible for these effects, leading us to hypothesize the existence of a novel EPO receptor.

What question did this study address?
The study sought to address whether a novel EPO receptor may exist. Based on the knowledge and analytics of our Dataome, we developed a bioinformatics pipeline to analyze every receptor in the human proteome for evidence that it may mediate EPO mediated cell survival. We identified EPHB4 as a novel EPO receptor and validated the functional, prognostic and therapeutic relevance of this gene using a combination of in vitro, in vivo and retrospective clinical studies.

What did this study add to our knowledge?
In this study, we identified a new mechanism that EphB4 acts as a critical mediator of erythropoietin signaling, which can induce tumor progression in cancer patients. Altogether our study provided a novel and clinically significant dimension to the biology of erythropoietin, which was not appreciated before.

How might this change drug discovery, development, and/or therapeutics?
The discovery resulted in a novel predictive biomarker for identifying patients who were more likely to experience poorer outcomes in response to rhEPO treatment (i.e. by virtue of high EPHB4 expression) and therefore be excluded from receiving this therapy. In addition, it also emphasized the relevance of EphB4 as an anti-cancer target and opened up the opportunity for a number of rational combination approaches with existing drugs (e.g. dasatinib).

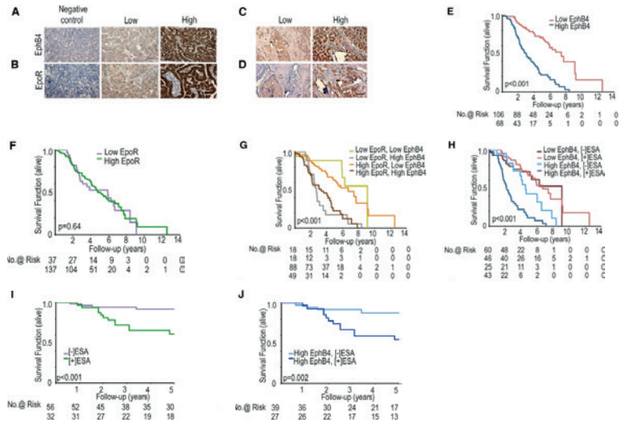


Figure: Clinical Relevance of EphB4 and EpoR Expression and ESA Treatment in Cancer Patients. (A–D) Representative immunohistochemical peroxidase staining for (A) EphB4 and (B) EpoR expression in ovarian cancer and (C) EphB4 and (D) EpoR expression in breast cancer samples.(E–G) Kaplan-Meier curves of disease-specific mortality for ovarian (E–H) and breast (I and J) cancer patients stratified by tumoral expression of (E) EphB4, (F) EpoR, or (G) both EphB4 and EpoR. (H) Evaluation of disease-specific survival duration of ovarian cancer patients based on ESA treatment and EphB4 expression. (I) Disease-specific survival analysis of breast cancer patients stratified by ESA treatment. (J) Disease-specific survival of breast cancer patients based on ESA treatment and EphB4 expression. The scale bar represents 50 µm.

For more information, see abstract number 19.

Journal

Cancer Cell

Reference

Cancer Cell. 2015 Nov 9;28(5):610-22. PMID: 26481148

2015

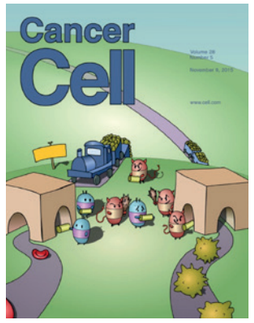
Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH EFFECT

MOLECULAR HEALTH GUIDE



We received Cancer Cell. The associated description is as follows "On the cover: Recombinant human erythropoietin (rhEpo, green bricks) has been used to relieve chemotherapy-induced anemia (left path; red blood cells shown in red). The possibility that rhEpo may promote tumor growth has been suggested, but the underlying mechanisms are not well understood. Pradeep et al. (pp. 610–622) identify EphB4 (red horned characters) as an alternative to the traditional erythropoietin receptor (EpoR; blue characters). Interaction of rhEpo and EphB4 triggers STAT3 signaling and promotes tumor growth and progression (right path; tumor shown in green).

Highlight

Genome guided treatment decision support using MH Guide

Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer.

What was the current knowledge on the topic prior to this work?
Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality in the USA and Europe and is predicted to become the second by 2030. The lack of treatment response to conventional therapeutic approaches as radiation and chemotherapy is attributable to many factors, including extrinsic or intrinsic resistance.

What question did this study address?
Pancreatic cancers may benefit from the developments in precision medicine, which has proven worthy elsewhere. In the present study, we aimed to investigate the clinical applicability of using NGS in combination with MH Guide to generate individualized analysis for a personalized approach for the treatment of pancreatic cancer.

What did this study add to our knowledge?
We demonstrated that NGS data in combination with evidence-based software analysis using MH Guide is feasible in the clinical setting of pancreatic cancer: unraveling novel treatment options and indicating important biomarkers of increased toxicity.

How might this change drug discovery, development, and/or therapeutics?
Results from this study provided the clinical rationale for the design of follow-on clinical studies (e.g. the PePaCaKa trial) designed to demonstrate the clinical utility of MH Guide in supporting treatment decision making for PDAC patients.

Journal

Molecular Oncology

Reference

Mol Oncol. 2017 Oct;11(10):1413-1429. PMID: 28675654

2017

Collaborator

Karolinska Institutet

Technology

MOLECULAR HEALTH GUIDE

For more information, see abstract number 25.

Highlight

Prediction of drug safety label evolution using MH Effect

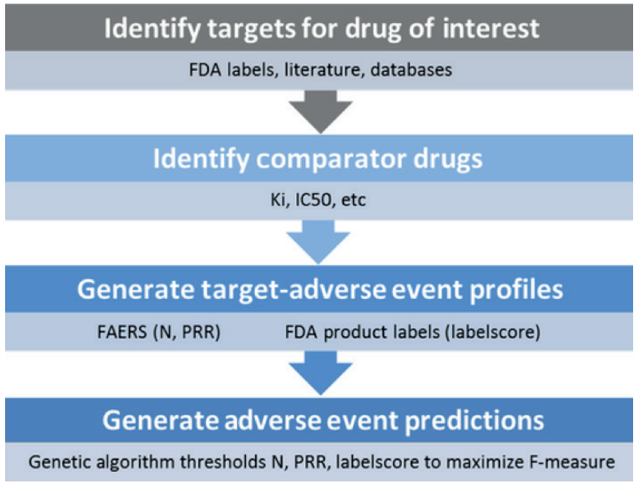
Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities.

What was the current knowledge on the topic prior to this work?
Predictive safety in the post-market setting at the FDA has relied upon expert review of available evidence from case reports, medical records, FAERS, and the literature. Systemic, quantitative methods were being evaluated.

What question did this study address?
We asked whether Target Adverse Event (TAE) profiles might improve the prediction of drug safety labels. The MH Effect technology provides TAE's i.e. aggregated drug AEs at the level of shared pharmacological targets. The study assessed the use of TAE profiles in anticipating significant postmarket drug AEs of interest.

What did this study add to our knowledge?
This study confirmed that aggregating AEs by pharmacological targets is predictive of postmarket AEs.

How might this change drug discovery, development, and/or therapeutics?
In addition to assisting with postmarket pharmacovigilance, this approach may also be used to anticipate AEs that may occur during drug development.



Showing the workflow for drug label prediction. MH Effect permitted the automated generation of Target Adverse Event profiles, a key element of this predictive workflow.

For more information, see abstract number 29.

Journal

An Official Journal of ASCPT and ISoP
CPT: Pharmacometrics & Systems Pharmacology

Reference

CPT Pharmacometrics Syst Pharmacol. 2018 Dec;7(12):809-817. PMID: 30354029

2018

Collaborator

FDA

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

MOLECULAR HEALTH EFFECT

1. Clinical and economic impact of the non-responder phenomenon-implications for systems based discovery.

Molecular diversity is a hallmark of life. Unfortunately, given that the clinical benefit of a drug can only be realized under certain genetic/molecular conditions, such heterogeneity can mean the difference between survival and death. For most targeted therapies it appears that such conditions are met in only a small percentage of patients, particularly in the monotherapy context. Notwithstanding, the nonresponder phenomenon can be viewed as a low-hanging fruit among medical needs, with a large body of scientific knowledge surrounding the target and the diseased system.

This knowledge, together with information about the molecular sources of nonresponse, provides a rational framework upon which novel intervention strategies can be built. Driven by such molecular considerations and the enormous economic implications, new levels of innovation are urgently required. Systems level patient characterization coupled with innovative in silico strategies hold great promise and suggest a future of theranostic-linked combination therapies, optimized cohort selection and rational prioritization of clinical opportunities.

Journal

DRUG DISCOVERY TODAY

Reference

Drug Discov Today. 2009 Apr; 14(7-8):380-5. PMID: 19200855

2009

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

2. Molecular perspectives on the non-responder phenomenon.

With the advent of targeted therapies promising to revolutionise the nature and success of patient care, the field of clinical oncology is facing a highly exciting future. While much of this enthusiasm comes from the hope for improved patient outcomes, a review of clinical response/relapse rates for current therapies provides a more sobering perspective. Given that the majority of patients are intrinsically resistant to the therapeutic potential of these molecules, efforts are now directed at characterising such non-responsive system behaviour and causative molecular insults.

Testament to this is an expanding catalogue of target and system-based aberrations, often defined through retrospective analyses of clinical tissue and associated outcome data. What has emerged is a complex picture, where numerous potential sources of cancer-specific aberration can contribute to refractory tumour behaviour. Clinicians, regulators and sponsors must now collaborate to determine how such knowledge should be used to enhance the clinical decision process and associated regulatory guidance.

Journal

DRUG DISCOVERY TODAY

Reference

Drug Discov Today. 2009 Apr; 14(7-8):373-9. PMID: 19200455

2009

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

3. Serum-based microRNAs: are we blinded by potential?

In a recent issue of PNAS, Mitchell et al. (1) reported exciting insights into the use of circulating microRNAs as biomarkers for cancer detection. Recently corroborated by similar studies, the potential now appears to extend well beyond the clinical oncology domain (2, 3). The observed specificity and simplicity of the approach are particularly striking and suggest that serum-based microRNAs could emerge as revolutionary sources of biomarker information. However, in the absence of thorough functional knowledge, might our focus on diagnostic potential be to the detriment of novel therapeutic opportunity?

The diagnostic specificity of circulating microRNAs supports the contention that they are not the molecular remnants of once-living tumor cells, but rather of utmost functional importance. This is consistent with the roles of other established biomarkers such as BCR-ABL or HER2, which further exemplify that modulation of "biomarker" function can produce efficacious therapeutic effects. Such perspective will no doubt encourage further hypotheses and experimentation, but perhaps one important speculation warrants immediate investigation. Might the secretion of specific microRNAs in cancer patients be a critical component of a tumor's molecular armamentarium? By affecting cellular systems elsewhere in the body, could the goal of such molecules be to produce a systemic environment that is conducive to disease progression? If true, such a mechanism would open an exciting therapeutic strategy involving the serum-based exchange of cancer-associated microRNAs for a healthy canonical complement. Not unlike the therapeutic premise of enzyme-replacement therapy, the concept should warrant immediate exploration by the microRNA community.

Journal

PNAS

Reference

Proc Natl Acad Sci U S A. 2009 Jan 6;106(1):E5 PMID: 19106287

2009

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

4. Drug profiling: knowing where it hits.

Off-target hits of drugs can lead to serious adverse effects or, conversely, to unforeseen alternative medical utility. Selectivity profiling against large panels of potential targets is essential for the drug discovery process to minimize attrition and maximize therapeutic utility. Lately, it has become apparent that drug promiscuity (polypharmacology) goes well beyond target families; therefore, lowering the profiling costs and expanding the coverage of targets is an industry-wide challenge to improve predictions. Here, we review current and promising drug profiling alternatives and commercial solutions in these exciting emerging fields.

Journal

DRUG DISCOVERY TODAY

Reference

Drug Discov Today. 2010 Sep;15(17-18):749-56.

2010

Collaborator

UCD DUBLIN

Technology

CLINICAL DATA DATAOME TECHNOLOGY MOLECULAR DATA

5. LAITOR - Literature assistant for identification of terms co-occurrences and relationships.

Biological knowledge is represented in scientific literature that often describes the function of genes/proteins (bioentities) in terms of their interactions (biointeractions). Such bioentities are often related to biological concepts of interest that are specific of a determined research field. Therefore, the study of the current literature about a selected topic deposited in public databases, facilitates the generation of novel hypotheses associating a set of bioentities to a common context.

We created a text mining system (LAITOR: Literature Assistant for Identification of Terms co-Occurrences and Relationships) that analyses co-occurrences of bioentities, biointeractions, and other biological terms in MEDLINE abstracts. The method accounts for the position of the co-occurring terms within sentences or abstracts. The system detected abstracts mentioning protein-protein interactions in a standard test (BioCreative II IAS test data) with a precision of 0.82-0.89 and a recall of 0.48-0.70. We illustrate the application of LAITOR to the detection of plant response genes in a dataset of 1000 abstracts relevant to the topic.
Text mining tools combining the extraction of interacting bioentities and biological concepts with network displays can be helpful in developing reasonable hypotheses in different scientific backgrounds.

Journal

BMC

Reference

BMC Bioinformatics. 2010 Feb 1;11:70. PMID:20122157

2010

Collaborator

MDC MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE IN THE HELMHOLTZ ASSOCIATION

Technology

DATAOME TECHNOLOGY — CLINICAL DATA — MOLECULAR DATA

6. EMT is the dominant program in human colon cancer.

Colon cancer has been classically described by clinicopathologic features that permit the prediction of outcome only after surgical resection and staging. We performed an unsupervised analysis of microarray data from 326 colon cancers to identify the first principal component (PC1) of the most variable set of genes. PC1 deciphered two primary, intrinsic molecular subtypes of colon cancer that predicted disease progression and recurrence.

Here we report that the most dominant pattern of intrinsic gene expression in colon cancer (PC1) was tightly correlated (Pearson R = 0.92, P < 10(-135)) with the EMT signature-- both in gene identity and directionality. In a global micro-RNA screen, we further identified the most anti-correlated microRNA with PC1 as MiR200, known to regulate EMT. These data demonstrate that the biology underpinning the native, molecular classification of human colon cancer--previously thought to be highly heterogeneous-- was clarified through the lens of comprehensive transcriptome analysis.

Journal

BMC

Reference

BMC Med Genomics. 2011 Jan 20;4:9. PMID: 21251323

2011

Collaborator

MOFFITT CANCER CENTER

Technology

MOLECULAR HEALTH GUIDE

7. Genetic determinants of anticancer drug activity: towards a global approach to personalized cancer medicine.

While current trials of anticancer agents serve to provide a population-based validation of therapeutic activity, clinical success is typically restricted to tumors of select molecular subtype. Recent insights have yielded a growing catalogue of germline and tumor-based aberrations that can predetermine whether a patient will achieve clinical benefit from a drug or not.

Thus, in order to realize the true potential of anticancer agents, we need to define the molecular contexts under which they will prove both efficacious and safe. In this article, we provide an overview of such molecular determinants and introduce the concept of 'cancer patient profiling' - the process and science of defining the optimal therapy for a given patient through the generation and analysis of system-wide molecular information.

Journal

EXPERT REVIEW

Reference

Expert Rev Mol Diagn. 2011 Jul;11(6):567-77. PMID: 21745011

2011

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

8. Intelligent clinical decision support systems for non-invasive bladder cancer diagnosis.

Currently, there are some paradigm shifts in medicine, from the search for a single ideal biomarker, to the search for panels of molecules, and from a reductionistic to a systemic view, placing these molecules on functional networks. There is also a general trend to favor non-invasive biomarkers. Identifying non-invasive biomarkers in high- throughput data, having thousands of features and only tens of samples is not trivial.

Here, we proposed a methodology and the related concepts to develop intelligent molecular biomarkers, via knowledge discovery in data, illustrated on bladder cancer diagno- sis. A knowledge discovery in data approach, with computational intelligence methods, is used to identify the relevant features and discover their relationships with the diagno- sis. The intelligent non-invasive diagnosis systems, is based on a team of mathematical models, discovered with genetic programming, and taking as inputs plasma microRNA.

This systems share with other intelligent systems we build, using this methodology but different computational/artificial intelligence techniques and clinical situations— chronic hepatitis, bladder cancer progression, and prostate cancer—the best published accuracy, even 100%. Computational intelligence could be a strong foundation for the newly emerging Knowledge-Based-Medicine. The impact of this paradigm shift on medical practice could be enormous. Instead of offering just hints or evidences to the clinicians, like Evidence-Based-Medicine, Knowledge-Based-Medicine which is made possible and co-exists with Evidence-Based-Medicine, offers intelligent clinical deci- sion supports systems.

Journal

Lecture Notes in Computer Science

Reference

Computational Intelligence Methods for Bioinformatics and Biostatistics

Volume 6685 of the series Lecture Notes in Computer Science pp 253-262

2011

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH GUIDE

9. Personalized cancer medicine-advances and socio-economic challenges.

It was Hippocrates, the father of Western medicine, who first emphasized the patient as the most important determinant of therapeutic efficacy. Although the principle of adjusting treatment to specific patient characteristics has since been the strategy of physicians, this is undermined by a population-biased approach to drug development.

Therefore, it is generally true to say that our current evidential approach to cancer treatment is driven more by drug-regulation requirements and market considerations than the specific needs of an individual patient. But, with cancer drug costs now spiraling out of control and the modest efficacy typically seen in patients, the community is again turning to Hippocrates' ancient paradigm--this time with emphasis on molecular considerations. Rapidly evolving technologies are empowering us to describe the molecular 'nature' of a patient and/or tumor and with this has come the beginning of truly personalized medicine, with maximized efficacy, cost effectiveness and hopefully improved survival for the patient.

Journal

nature REVIEWS CLINICAL ONCOLOGY

Reference

Nat Rev Clin Oncol. 2011 Oct 11;8(12):735-41: PMID: 21989071

2011

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH GUIDE

10. Using graph theory to analyze biological networks.

Understanding complex systems often requires a bottom-up analysis towards a systems biology approach. The need to investigate a system, not only as individual components but as a whole, emerges. This can be done by examining the elementary constituents individually and then how these are connected. The myriad components of a system and their interactions are best characterized as networks and they are mainly represented as graphs where thousands of nodes are connected with thousands of vertices.

In this article we demonstrate approaches, models and methods from the graph theory universe and we discuss ways in which they can be used to reveal hidden properties and features of a network. This network profiling combined with knowledge extraction will help us to better understand the biological significance of the system.

Journal

BMC

BioData Mining

Reference

BioData Min. 2011 Apr 28;4:10 PMID:21527005

2011

Collaborator

Technology

11. A scatter-based prototype framework and multi-class extension of support vector machines.

We provide a novel interpretation of the dual of support vector machines (SVMs) in terms of scatter with respect to class prototypes and their mean. As a key contribution, we extend this framework to multiple classes, providing a new joint Scatter SVM algorithm, at the level of its binary counterpart in the number of optimization variables.

This enables us to implement computationally efficient solvers based on sequential minimal and chunking optimization. As a further contribution, the primal problem formulation is developed in terms of regularized risk minimization and the hinge loss, revealing the score function to be used in the actual classification of test patterns. We investigate Scatter SVM properties related to generalization ability, computational efficiency, sparsity and sensitivity maps, and report promising results.

Journal

PLOS ONE

Reference

Plos One 7(10): e42947. PMID:23118845

2012

Collaborator

THE ARCTIC UNIVERSITY OF NORWAY · UIT ·

Technology

12. Biggest challenges in bioinformatics.

The third Heidelberg Unseminars in Bioinformatics (HUB) was held on 18th October 2012, at Heidelberg University, Germany. HUB brought together around 40 bioinformaticians from academia and industry to discuss the 'Biggest Challenges in Bioinformatics' in a 'World Café' style event.

Journal

EMBO reports

Reference

EMBO Rep. 2013 Apr;14(4):302-4 PMID:23492829

2013

Collaborator

EMBL-EBI

Technology

13. Systemic microRNA measurement, a useful tool for predicting diagnosis in bladder cancer.

Bladder cancer (BC) is a burdensome disease with significant morbidity, mortality, and cost. The development of novel plasma-based biomarkers for BC diagnosis and surveillance could significantly improve clinical outcomes and decrease health expenditures. Plasma miRNAs are promising biomarkers that have yet to be rigorously investigated in BC. To determine the feasibility and efficacy of detecting BC with plasma miRNA signatures. Plasma miRNA was isolated from 20 patients with bladder cancer and 18 noncancerous controls.

Samples were analyzed with a miRNA array containing duplicate probes for each miRNA in the Sanger database. Logistic regression modeling was used to optimize diagnostic miRNA signatures to distinguish between muscle invasive BC (MIBC), non-muscle-invasive BC (NMIBC) and noncancerous controls. Seventy-nine differentially expressed plasma miRNAs (local false discovery rate [FDR] <0.5) in patients with or without BC were identified. Some diagnostically relevant miRNAs, such as miR-200b, were up-regulated in MIBC patients, whereas others, such as miR-92 and miR-33, were inversely correlated with advanced clinical stage, supporting the notion that miRNAs released in the circulation have a variety of cellular origins.

Logistic regression modeling was able to predict diagnosis with 89% accuracy for detecting the presence or absence of BC, 92% accuracy for distinguishing invasive BC from other cases, 100% accuracy for distinguishing MIBC from controls, and 79% accuracy for three-way classification between MIBC, NIMBC, and controls.

This study provides preliminary data supporting the use of plasma miRNAs as a noninvasive means of BC detection. Future studies will be required to further specify the optimal plasma miRNA signature, and to apply these signatures to clinical scenarios, such as initial BC detection and BC surveillance.

Journal

UROLOGIC ONCOLOGY
Seminars and Original Investigations

Reference

Urol Oncol. 2013 Nov;31(8):1701-8 PMID: 22863868

2013

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH GUIDE

14. Src activation by β-adrenoreceptors is a key switch for tumour metastasis.

Noradrenaline can modulate multiple cellular functions important for cancer progression; however, how this single extracellular signal regulates such a broad array of cellular processes is unknown. Here we identify Src as a key regulator of phosphoproteomic signalling networks activated in response to beta-adrenergic signalling in cancer cells.

These results also identify a new mechanism of Src phosphorylation that mediates beta-adrenergic/PKA regulation of downstream networks, thereby enhancing tumour cell migration, invasion and growth. In human ovarian cancer samples, high tumoural noradrenaline levels were correlated with high pSrc(Y419) levels. Moreover, among cancer patients, the use of beta blockers was significantly associated with reduced cancer-related mortality. Collectively, these data provide a pivotal molecular target for disrupting neural signalling in the tumour microenvironment.

Journal

nature COMMUNICATIONS

Reference

Nat Commun. 2013;4:1403. PMID: 23360994

2013

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH EFFECT

15. Drugs highly associated with Infusion reactions reported using two different data-mining methodologies.

Infusion reactions can be serious life threatening adverse events and have been associated with many drugs and biologic agents. Our objective was to report drugs associated with infusion reactions using two different data-mining methodologies.

The Food and Drug Administration Adverse Event Reporting System (FAERS) was data-mined for drugs highly associated with infusion reactions. Drugs were included if there were >10 reported adverse events and if the Empirical Bayesian Geometric Mean (EBGM) score ≥ 2. Molecular Health's MASE (Molecular Analysis of Side Effects) reports Proportional Reporting Ratios (PRR) for drugs highly associated with infusion reactions and was cross-referenced to improve detection sensitivity.

Using FAERS, the highest EBGM scores by class were reported as: pegloticase and α-1-antitrypsyn (enzymes), iron dextran and ferric gluconate (electrolytes and nutrients), infliximab and gemtuzumab (immunomodulators), and paclitaxel and oxaliplatin (antimetabolites). Using MASE, the highest PRR scores were reported as: idursulfase and galsulfase (enzymes), iron dextran and phytonadione (electolytes and nutrients), gemtuzumab and infliximab (immunomodulators), mercaptopurine and azathioprine (antimetabolites). Amphotericin and vancomycin had the highest scores for the antimicrobial class for both FAERS and MASE. Using the two statistical methods EBGM and PRR, both specificity and sensitivity were preserved.

However, neither system detected several drugs with established relationships to infusion reactions, including protamine and nitroglycerine. Reactions caused by these drugs were possibly underreported because the effects have been well established or due to evolution of administration with slower administration. We hope this analysis encourages further research into overlapping mechanisms for infusion reactions.

Journal

Journal of Blood Disorders & Transfusion
ISSN: 2155-9864

Reference

J Blood Disord Transfus 5:195. doi: 10.4172/2155-9864.1000195

2014

Collaborator

FDA

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

MOLECULAR HEALTH EFFECT

16. Data mining FAERS to analyse molecular targets highly associated with Stevens Johnson Syndrome.

Drug features that are associated with Stevens-Johnson syndrome (SJS) have not been fully characterized. A molecular target analysis of the drugs associated with SJS in the FDA Adverse Event Reporting System (FAERS) may contribute to mechanistic insights into SJS pathophysiology. The publicly available version of FAERS was analyzed to identify disproportionality among the molecular targets, metabolizing enzymes, and transporters for drugs associated with SJS.

The FAERS in-house version was also analyzed for an internal comparison of the drugs most highly associated with SJS. Cyclooxygenases 1 and 2, carbonic anhydrase 2, and sodium channel 2 alpha were identified as disproportionately associated with SJS. Cytochrome P450 (CYPs) 3A4 and 2C9 are disproportionately represented as metabolizing enzymes of the drugs associated with SJS adverse event reports. Multidrug resistance protein 1 (MRP-1), organic anion transporter 1 (OAT1), and PEPT2 were also identified and are highly associated with the transport of these drugs.

A detailed review of the molecular targets identifies important roles for these targets in immune response. The association with CYP metabolizing enzymes suggests that reactive metabolites and oxidative stress may have a contributory role. Drug transporters may enhance intracellular tissue concentrations and also have vital physiologic roles that impact keratinocyte proliferation and survival. Data mining FAERS may be used to hypothesize mechanisms for adverse drug events by identifying molecular targets that are highly associated with drug-induced adverse events. The information gained may contribute to systems biology disease models.

Journal

Journal of Medical Toxicology

Reference

J Med Toxicol. 2015 Jun;11 (2):265-73. doi: 10.1007/s13181-015-0472-1. PMID:25876064

2015

Collaborator

FDA

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

MOLECULAR HEALTH EFFECT

17. How to learn about gene function: text-mining or ontologies?

As the amount of genome information increases rapidly, there is a correspondingly greater need for methods that provide accurate and automated annotation of gene function. For example, many high-throughput technologies--e.g., next-generation sequencing--are being used today to generate lists of genes associated with specific conditions. However, their functional interpretation remains a challenge and many tools exist trying to characterize the function of gene-lists. Such systems rely typically in enrichment analysis and aim to give a quick insight into the underlying biology by presenting it in a form of a summary-report.

While the load of annotation may be alleviated by such computational approaches, the main challenge in modern annotation remains to develop a systems form of analysis in which a pipeline can effectively analyze gene-lists quickly and identify aggregated annotations through computerized resources. In this article we survey some of the many such tools and methods that have been developed to automatically interpret the biological functions underlying gene-lists. We overview current functional annotation aspects from the perspective of their epistemology (i.e., the underlying theories used to organize information about gene function into a body of verified and documented knowledge) and find that most of the currently used functional annotation methods fall broadly into one of two categories: they are based either on 'known' formally-structured ontology annotations created by 'experts' (e.g., the GO terms used to describe the function of Entrez Gene entries), or--perhaps more adventurously--on annotations inferred from literature (e.g., many text-mining methods use computer-aided reasoning to acquire knowledge represented in natural languages).

Overall however, deriving detailed and accurate insight from such gene lists remains a challenging task, and improved methods are called for. In particular, future methods need to (1) provide more holistic insight into the underlying molecular systems; (2) provide better follow-up experimental testing and treatment options, and (3) better manage gene lists derived from organisms that are not well-studied. We discuss some promising approaches that may help achieve these advances, especially the use of extended dictionaries of biomedical concepts and molecular mechanisms, as well as greater use of annotation benchmarks.

Journal

METHODS

Reference

Methods. 2015 Mar;74:3-15. PMID:25088781

2015

Collaborator

Garvan Institute of Medical Research

Technology

DATAOME TECHNOLOGY — CLINICAL DATA — MOLECULAR DATA

18. Relationships of clinical response to relevant molecular signal during Phase I testing of Aurora Kinase A inhibitor: Retrospective assessment.

Retrospective analysis utilizing "next generation sequencing (NGS)" was done on cancer tissue harvested from 14 patients prior to receiving MLN8237, a novel Aurora Kinase A inhibitor. The responding patients (n=4) were characterized by stable disease ≥6 months and prolonged time of progression (≥1.3 fold prior treatment). Differential patterns of nodal connectivity in protein-protein interaction networks (consequent to determined genomic alterations) emerged from the comparison between responder and non-responder groups.

The responding patient population showed high connectivity within MYC related genes including regulators of the Wnt/beta-catenin pathway. On the other hand, the non-responding patients showed high connectivity centered on the TP53/RB1 axis. Matching "targeted therapy to target" is a sine qua non for maximizing effective therapy in appropriate patients and NGS mapping may further our understanding of the relationships between molecular biological pathways and targeted therapy response.

While awaiting further progress in systems analysis across "omic" levels (genomic-transcriptomic-proteomic), research involving of NGS sequence mapping to interrogate patient response to therapy in order to help elucidate molecular therapeutic predictors is justified based on the urgent needs of patient care.

Journal

Reference

Integrative Molecular Medicine: DOI: 10.15761/IMM.1000162

2015

Collaborator

MARY CROWLEY CANCER RESEARCH
HOPE LIVES HERE™

Technology

MOLECULAR HEALTH GUIDE

19. Erythropoietin Stimulates Tumor Growth via EphB4.

While recombinant human erythropoietin (rhEpo) has been widely used to treat anemia in cancer patients, concerns about its adverse effects on patient survival have emerged. A lack of correlation between expression of the canonical EpoR and rhEpo's effects on cancer cells prompted us to consider the existence of an alternative Epo receptor. Here, we identified EphB4 as an Epo receptor that triggers downstream signaling via STAT3 and promotes rhEpo-induced tumor growth and progression.

In human ovarian and breast cancer samples, expression of EphB4 rather than the canonical EpoR correlated with decreased disease-specific survival in rhEpo-treated patients. These results identify EphB4 as a critical mediator of erythropoietin-induced tumor progression and further provide clinically significant dimension to the biology of erythropoietin.

Journal

Cancer Cell

Reference

Cancer Cell. 2015 Nov 9;28(5):610-22. PMID: 26481148

2015

Collaborator

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Technology

MOLECULAR HEALTH EFFECT

MOLECULAR HEALTH GUIDE

20. Improving drug safety with a systems pharmacology approach.

Systems pharmacology is used to mechanistically analyze drug-adverse drug reaction (ADRs) pairs and is a promising solution to the complex problem of understanding mechanisms of toxicity. In this research, we have explored the feasibility of retrospectively mapping population-level adverse events from the FDA Adverse Event Reporting System (FAERS) to chemical and biological databases to identify drug safety signals and the underlying molecular mechanisms. We used an analytic platform - Molecular Analysis of Side Effects (MASE™).

For this purpose, we selected the adverse event of severe and potentially fatal cutaneous reactions (SCARs) that are associated with acetaminophen (APAP). SCARs encompass the continuum between Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). We found a statistically significant association between APAP and TEN, the most severe form of SCARs. We also explored the influence of APAP on other classes of drugs commonly associated with SCARs. We found that APAP significantly reduced the risk of SCARs commonly associated with carbamazepine (CBZ).

We used molecular docking simulations to propose a mechanism for APAP's reduction in CBZ-induced SCARs which is competitive inhibition of the binding of CBZ to HLA-B*15:02. We conclude that systems pharmacology can complement established surveillance methodologies by providing a means to undertake an independent investigation and review of the mechanisms by which drugs cause adverse events.

Journal

Reference

Eur J Pharm Sci. 2016 Oct 30;94:84-92. doi: 10.1016/j.ejps.2016.06.009 PMID:27287422

2016

Collaborator

UF UNIVERSITY of FLORIDA

Technology

MOLECULAR HEALTH EFFECT

21. Use of “big data” in drug discovery and clinical trials.

Oncology is undergoing a data-driven metamorphosis. Armed with new and ever more efficient molecular and information technologies, we have entered an era where data is helping us spearhead the fight against cancer. This technology driven data explosion, often referred to as “big data”, is not only expediting biomedical discovery, but it is also rapidly transforming the practice of oncology into an information science.

This evolution is critical, as results to-date have revealed the immense complexity and genetic heterogeneity of patients and their tumors, a sobering reminder of the challenge facing every patient and their oncologist. This can only be addressed through development of clinico-molecular data analytics that provide a deeper understanding of the mechanisms controlling the biological and clinical response to available therapeutic options. Beyond the exciting implications for improved patient care, such advancements in predictive and evidence-based analytics stand to profoundly affect the processes of cancer drug discovery and associated clinical trials.

Journal

GYNECOLOGIC ONCOLOGY

Reference

Gynecol Oncol. 2016 Apr;141(1):17-23. PMID: 27016224

2016

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

22. A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC.

Colorectal cancer (CRC) is a highly heterogeneous disease, for which prognosis has been relegated to clinicopathologic staging for decades. There is a need to stratify subpopulations of CRC on a molecular basis to better predict outcome and assign therapies.

Here we report targeted exome-sequencing of 1,321 cancer-related genes on 468 tumour specimens, which identified a subset of 17 genes that best classify CRC, with APC playing a central role in predicting overall survival. APC may assume 0, 1 or 2 truncating mutations, each with a striking differential impact on survival. Tumours lacking any APC mutation carry a worse prognosis than single APC mutation tumours; however, two APC mutation tumours with mutant KRAS and TP53 confer the poorest survival among all the subgroups examined. Our study demonstrates a prognostic role for APC and suggests that sequencing of APC may have clinical utility in the routine staging and potential therapeutic assignment for CRC.

Journal

nature COMMUNICATIONS

Reference

Nat. Commun. 7, 11743. doi:10.1038/ncomms11743 PMID: 27302369

2016

Collaborator

Gibbs Cancer Center & Research Institute

Technology

MOLECULAR HEALTH GUIDE

23. Reliability of algorithmic somatic copy number alteration detection from targeted capture data.

Whole exome and gene panel sequencing are increasingly used for oncological diagnostics. To investigate the accuracy of SCNA detection algorithms on simulated and clinical tumor samples, the precision and sensitivity of four SCNA callers were measured using 50 simulated whole exome and 50 simulated targeted gene panel datasets, and using 119 TCGA tumor samples for which SNP array data were available. On synthetic exome and panel data, VarScan2 mostly called false positives, whereas Control-FREEC was precise (>90% correct calls) at the cost of low sensitivity (<40% detected). ONCOCNV was slightly less precise on gene panel data, with similarly low sensitivity.

This could be explained by low sensitivity for amplifications and high precision for deletions. Surprisingly, these results were not strongly affected by moderate tumor impurities; only contaminations with more than 60% non-cancerous cells resulted in strongly declining precision and sensitivity. On the 119 clinical samples, both Control-FREEC and CNVkit called 71.8% and 94%, respectively, of the SCNAs found by the SNP arrays, but with a considerable amount of false positives (precision 29% and 4.9%). Whole exome and targeted gene panel methods by design limit the precision of SCNA callers, making them prone to false positives. SCNA calls cannot easily be integrated in clinical pipelines that use data from targeted capture-based sequencing. If used at all, they need to be cross-validated using orthogonal methods.

Journal

Bioinformatics

Reference

Bioinformatics. 2017 Sep 15;33(18):2791-2798. PMID: 28472276

2017

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

24. Comprehensive benchmarking of SNV callers for highly admixed tumors.

Precision medicine attempts to individualize cancer therapy by matching tumor-specific genetic changes with effective targeted therapies. A crucial first step in this process is the reliable identification of cancer-relevant variants, which is considerably complicated by the impurity and heterogeneity of clinical tumor samples. We compared the impact of admixture of non-cancerous cells and low somatic allele frequencies on the sensitivity and precision of 19 state-of-the-art SNV callers. We studied both whole exome and targeted gene panel data and up to 13 distinct parameter configurations for each tool. We found vast differences among callers.

Based on our comprehensive analyses we recommend joint tumor-normal calling with MuTect, EBCall or Strelka for whole exome somatic variant calling, and HaplotypeCaller or FreeBayes for whole exome germline calling. For targeted gene panel data on a single tumor sample, LoFreqStar performed best. We further found that tumor impurity and admixture had a negative impact on precision, and in particular, sensitivity in whole exome experiments. At admixture levels of 60% to 90% sometimes seen in pathological biopsies, sensitivity dropped significantly, even when variants were originally present in the tumor at 100% allele frequency. Sensitivity to low-frequency SNVs improved with targeted panel data, but whole exome data allowed more efficient identification of germline variants. Effective somatic variant calling requires high-quality pathological samples with minimal admixture, a consciously selected sequencing strategy, and the appropriate variant calling tool with settings optimized for the chosen type of data.

Journal

PLOS ONE

Reference

PLoS One. 2017 Oct 11;12(10):e0186175. PMID: 29020110

2017

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

25. Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) is a tumor with an extremely poor prognosis, predominantly as a result of chemotherapy resistance and numerous somatic mutations. Consequently, PDAC is a prime candidate for the use of sequencing to identify causative mutations, facilitating subsequent administration of targeted therapy. In a feasibility study, we retrospectively assessed the therapeutic recommendations of a novel, evidence-based software that analyzes next-generation sequencing (NGS) data using a large panel of pharmacogenomic biomarkers for efficacy and toxicity. Tissue from 14 patients with PDAC was sequenced using NGS with a 620 gene panel. FASTQ files were fed into treatmentmap.

The results were compared with chemotherapy in the patients, including all side effects. No changes in therapy were made. Known driver mutations for PDAC were confirmed (e.g. KRAS, TP53). Software analysis revealed positive biomarkers for predicted effective and ineffective treatments in all patients. At least one biomarker associated with increased toxicity could be detected in all patients. Patients had been receiving one of the currently approved chemotherapy agents. In two patients, toxicity could have been correctly predicted by the software analysis. The results suggest that NGS, in combination with an evidence-based software, could be conducted within a 2-week period, thus being feasible for clinical routine. Therapy recommendations were principally off-label use.

Based on the predominant KRAS mutations, other drugs were predicted to be ineffective. The pharmacogenomic biomarkers indicative of increased toxicity could be retrospectively linked to reported negative side effects in the respective patients. Finally, the occurrence of somatic and germline mutations in cancer syndrome-associated genes is noteworthy, despite a high frequency of these particular variants in the background population. These results suggest software-analysis of NGS data provides evidence-based information on effective, ineffective and toxic drugs, potentially forming the basis for precision cancer medicine in PDAC.

Journal

Molecular Oncology

Reference

Mol Oncol. 2017 Oct;11(10):1413-1429. PMID: 28675654

2017

Collaborator

Karolinska Institutet

Technology

MOLECULAR HEALTH GUIDE

26. Association between serotonin syndrome and second-generation antipsychotics via pharmacological target-adverse event analysis.

Case reports suggest an association between second-generation antipsychotics (SGAs) and serotonin syndrome (SS). The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) was analyzed to generate hypotheses about how SGAs may interact with pharmacological targets associated with SS. FAERS was integrated with additional sources to link information about adverse events with drugs and targets.

Using Proportional Reporting Ratios, we identified signals that were further investigated with the literature to evaluate mechanistic hypotheses formed from the integrated FAERS data. Analysis revealed common pharmacological targets perturbed in both SGA and SS cases, indicating that SGAs may induce SS. The literature also supported 5-HT2A antagonism and 5-HT1A agonism as common mechanisms that may explain the SGA-SS association. Additionally, integrated FAERS data mining and case studies suggest that interactions between SGAs and other serotonergic agents may increase the risk for SS. Computational analysis can provide additional insights into the mechanisms underlying the relationship between SGAs and SS.

Journal

CTS Clinical and Translational Science

Reference

Clin Transl Sci. 2018 May;11(3):322-329. PMID: PMID: 29575568

2018

Collaborator

FDA

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

MOLECULAR HEALTH EFFECT

27. In silico profiling of clinical phenotypes for human targets using adverse event data.

We present a novel approach for the molecular transformation and analysis of patient clinical phenotypes. Building on the fact that drugs perturb the function of targets/genes, we integrated data from 8.2 million clinical reports detailing drug-induced side effects with the molecular world of drug-target information. Using this dataset, we extracted 1.8 million associations of clinical phenotypes to 770 human drug-targets. This collection is perhaps the largest phenotypic profiling reference of human targets to-date, and unique in that it enables rapid development of testable molecular hypotheses directly from human-specific information.

We also present validation results demonstrating analytical utilities of the approach, including drug safety prediction, and the design of novel combination therapies. Challenging the long-standing notion that molecular perturbation studies cannot be performed in humans, our data allows researchers to capitalize on the vast tomes of clinical information available throughout the healthcare system.

Journal

high throughput

Reference

High Throughput. 2018 Nov 23;7(4). PMID: 30477159

2018

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH EFFECT

28. A neural autoencoder approach for document ranking and query refinement in pharmacogenomic information retrieval.

In this study, we investigate learning-to-rank and query refinement approaches for information retrieval in the pharmacogenomic domain. The goal is to improve the information retrieval process of biomedical curators, who manually build knowledge bases for personalized medicine.

We study how to exploit the relationships between genes, variants, drugs, diseases and outcomes as features for document ranking and query refinement. For a supervised approach, we are faced with a small amount of annotated data and a large amount of unannotated data. Therefore, we explore ways to use a neural document auto-encoder in a semi-supervised approach. We show that a combination of established algorithms, feature-engineering and a neural auto-encoder model yield promising results in this setting.

Journal

Proceedings of the BioNLP 2018 workshop

Reference

https://www.aclweb.org/anthology/W18-2310.pdf

2018

Collaborator

UNIVERSITY OF MANNHEIM

Technology

CLINICAL DATA – DATAOME TECHNOLOGY – MOLECULAR DATA

29. Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities.

Clinical trials can fail to detect rare adverse events (AEs). We assessed the ability of pharmacological target adverse-event (TAE) profiles to predict AEs on US Food and Drug Administration (FDA) drug labels at least 4 years after approval. TAE profiles were generated by aggregating AEs from the FDA adverse event reporting system (FAERS) reports and the FDA drug labels for drugs that hit a common target. A genetic algorithm (GA) was used to choose the adverse event (AE) case count (N), disproportionality score in FAERS (proportional reporting ratio (PRR)), and percent of comparator drug labels with an AE to maximize F-measure.

With FAERS data alone, precision, recall, and specificity were 0.57, 0.78, and 0.61, respectively. After including FDA drug label data, precision, recall, and specificity improved to 0.67, 0.81, and 0.71, respectively. Eighteen of 23 (78%) postmarket label changes were identified correctly. TAE analysis shows promise as a method to predict AEs at the time of drug approval.

Journal

CPT: Pharmacometrics & Systems Pharmacology

Reference

CPT Pharmacometrics Syst Pharmacol. 2018 Dec;7(12):809-817. PMID: 30354029

2018

Collaborator

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

MOLECULAR HEALTH EFFECT

30. Adverse event circumstances and the case of drug interactions.

Adverse events are a common and for the most part unavoidable consequence of therapeutic intervention. Nevertheless, available tomes of such data now provide us with an invaluable opportunity to study the relationship between human phenotype and drug-induced protein perturbations within a patient system. Deciphering the molecular basis of such adverse responses is not only paramount to the development of safer drugs but also presents a unique opportunity to dissect disease systems in search of novel response biomarkers, drug targets, and efficacious combination therapies.

Inspired by the potential applications of this approach, we first examined adverse event circumstances reported in FAERS and then performed a molecular level interrogation of cancer patient adverse events to investigate the prevalence of drug-drug interactions in the context of patient responses. We discuss avoidable and/or preventable cases and how molecular analytics can help optimize therapeutic use of co-medications. While up to one out of three adverse events in this dataset might be explicable by iatrogenic, patient, and product/device related factors, almost half of the patients in FAERS received multiple drugs and one in four may have experienced effects attributable to drug interactions.

Journal

healthcare

Reference

Healthcare (Basel). 2019 Mar 19;7(1):45. PMID: 30893930

2019

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH EFFECT

31. Precision Oncology - The quest for evidence.

The molecular characterization of patient tumors provides a rational and highly promising approach for guiding oncologists in treatment decision-making. Notwithstanding, genomic medicine still remains in its infancy, with innovators and early adopters continuing to carry a significant portion of the clinical and financial risk. Numerous innovative precision oncology trials have emerged globally to address the associated need for evidence of clinical utility.

These studies seek to capitalize on the power of predictive biomarkers and/or treatment decision support analytics, to expeditiously and cost-effectively demonstrate the positive impact of these technologies on drug resistance/response, patient survival, and/or quality of life. Here, we discuss the molecular foundations of these approaches and highlight the diversity of innovative trial strategies that are capitalizing on this emergent knowledge. We conclude that, as increasing volumes of clinico-molecular outcomes data become available, in future, we will begin to transition away from expert systems for treatment decision support (TDS), towards the power of AI-assisted TDS-an evolution that may truly revolutionize the nature and success of cancer patient care.

Journal

Journal of Personalized Medicine

Reference

J Pers Med. 2019 Sep 5;9(3). pii: E43.n PMID: 31492009

2019

Collaborator

MOLECULAR HEALTH

Technology

MOLECULAR HEALTH GUIDE

32. Radioimmunotherapy in non-Hodgkin's Lymphoma: Retrospective adverse event profiling of zevalin and bexxar.

The development of monoclonal antibodies has dramatically changed the outcome of patients with non-Hodgkin's lymphoma (NHL), the most common hematological malignancy. However, despite the satisfying results of monoclonal antibody treatment, only few NHL patients are permanently cured with single-agent therapies. In this context, radioimmunotherapy, the administration of radionuclides conjugated to monoclonal antibodies, is aimed to augment the single-agent efficacy of immunotherapy in order to deliver targeted radiation to tumors, particularly CD20+ B-cell lymphomas.

Based on evidence from several trials in NHL, the radiolabeled antibodies 90Y-ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals) and 131I-tositumomab (Bexxar, GlaxoSmithKline) received FDA approval in 2002 and 2003, respectively. However, none of the two radioimmunotherapeutic agents has been broadly applied in clinical practice. The main reason for the under-utilization of radioimmunotherapy includes economic and logistic considerations. However, concerns about potential side effects have also been raised. Driven by these developments, we performed retrospective analysis of adverse events reporting Zevalin or Bexxar, extracted from the FDA's Adverse Event Reporting System (FAERS) and the World Health Organization's VigiBase repository.

Our results indicate that the two radioimmunotherapeutic agents have both related and distinct side effect profiles and confirm their known toxicological considerations. Our work also suggests that computational analysis of real-world post-marketing data can provide informative clinical insights. While more prospective studies are necessary to fully characterize the efficacy and safety of radioimmunotherapy, we expect that it has not yet reached its full therapeutic potential in modern hematological oncology.

Journal

pharmaceuticals

Reference

Pharmaceuticals 2019, 12(4), 141

2019

Collaborator

INSELSPITAL UNIVERSITÄTSSPITAL BERN HÔPITAL UNIVERSITAIRE DE BERNE

Technology

MOLECULAR HEALTH EFFECT

MOLECULAR HEALTH

Better data. Better insights.
Better outcomes.
molecularhealth.com

Molecular Health GmbH
Kurfuersten-Anlage 21
69115 Heidelberg
Germany

For further information please contact:

Dr. David B. Jackson
David.Jackson@molecularhealth.com

MH-19-060-1