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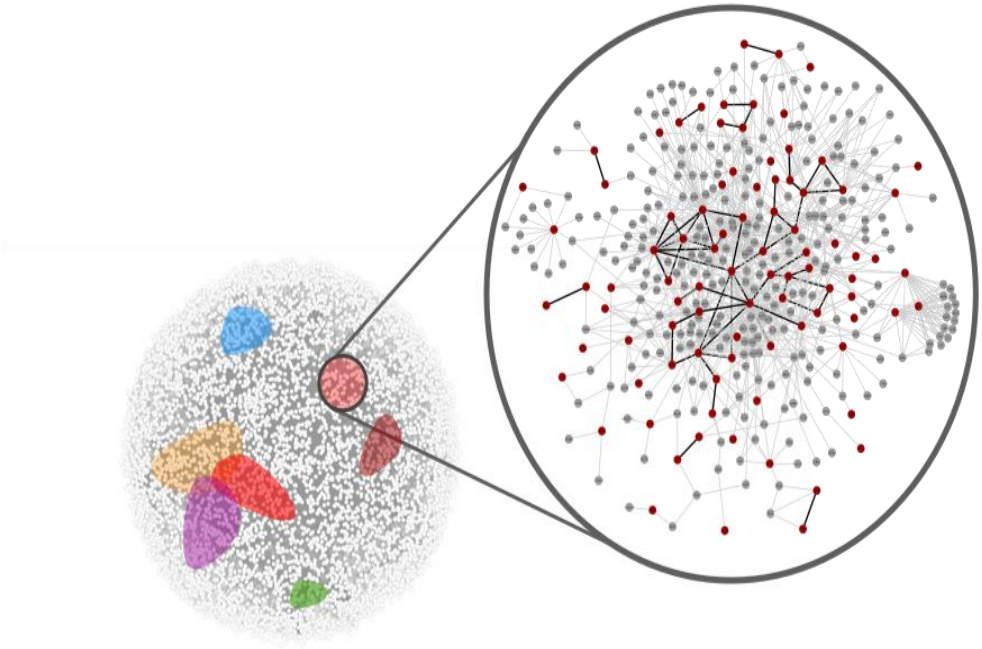
Second International Conference on Network Medicine and Big Data



April 12-13, 2021

Virtual/Boston, MA

Hosted by:

Brigham and Women's Hospital

and

Harvard Medical School

Boston, MA (USA)

Second International Conference on Network Medicine and Big Data

*[Hosted virtually by **Brigham and Women's Hospital**]*

April 12-13, 2021 – Boston, Massachusetts, USA

Harvard Medical School

NOTE: All times listed are Eastern/USA time zone

Day 1 - Session I: General Principles

Co-Moderators: Joseph Loscalzo and Paola Velardi

7:45-7:50 **Welcome**
Joseph Loscalzo
(Brigham/Harvard)
and

7:50-8:00 **Welcome**
George Q. Daley
(Dean, Harvard Medical School)

8:00-8:45 **Interactome Variants, Personalized Reticulotypes, and Precision Medicine**
Joseph Loscalzo (Brigham/Harvard)

8:45-9:05 **Why Bother With Networks**
John Quackenbush (Brigham/Harvard School of Public Health)

9:05-9:25 **Ontological and Connectivity Structure of Disease-Gene Modules in the Human Interactome**
Paola Velardi (University of Rome Sapienza)

9:25-9:45 **Cells, Tissues, and Regulatory Networks**
Kimberly Glass (Brigham/Harvard)

9:45-10:00 Break

10:00-10:20 **Biochemical Networks and Redox Biology**
Dean Jones (Emory)

10:20-10:40 **Visualizing Networks**
Joerg Menche (Max Perutz Labs, University of Vienna, Austria)

10:40-11:00 **Networks and the Foodome**
Albert-Laszlo Barabasi (Northeastern University)

11:00-11:20 **Predicting Signed Interactions, Including Drug Combinations and Genetic Interactions**
Istvan Kovacs (Northwestern)

11:20-11:35 **Open Discussion**

11:35-12:30 **LUNCH Break**

Session II: Disease Phenotyping
Co-Moderators: Bradley A. Maron & George Washko

12:30-12:50 **Orthogonal Phenotyping and Disease Definition**
Calum MacRae (Brigham/Harvard)

12:50-1:10 **Complex Phenotypes and Genomics**
Jake Lusis (UCLA)

1:10-1:30 **Network Medicine and Personalized Disease Phenotype**
Bradley Maron (Brigham/Harvard)

1:30-1:50 **PPI Prediction Challenge Update**
Yang-Yu Liu and Paola Velardi

1:50-2:10 **Network-based Approaches for the Identification of Cancer Signatures from Omics Data**
Paola Paci (University of Rome Sapienza)

2:10-2:30 **Big Data and the Comorbidity Landscape**
Isaac Kohane (Harvard Medical School)

2:30-2:50 Break

2:50-3:10 **Disease Trajectories and Precision Medicine**
Soren Brunak (University of Copenhagen)

3:10-3:30 **Quantitative Phenotype Imaging**
George Washko (Brigham/Harvard)

3:30-3:50 **Brain Network Topology Maps and the Dysfunctional Substrate of Cognitive Processes in Schizophrenia**
Guido Caldarelli (University of Rome Sapienza/University of Venice)

3:50-4:10 **Predicting Drug Response and Synergy using Deep Learning Models of Human Disease**
Trey Ideker (UCSD)

4:10-4:30 **Open Discussion**

Day 2: Session III: Drug Development
Co-Moderators: Feixiong Cheng and Harald Schmidt

8:00-8:20 **Network Pharmacology**
Harald Schmidt (Maastricht University, Netherlands)

8:20-8:40 **Systems Pharmacology and Drug Repurposing**
Ravi Iyengar (Mt. Sinai School of Medicine, NY)

8:40-9:00 **High Performance Computing and Unbiased Drug-Target Identification**
Felice Lightstone (Lawrence Livermore National Laboratory)

9:00-9:20 **Network Medicine and Drug Repurposing in Alzheimer's Disease**
Feixiong Cheng (Cleveland Clinic)

9:20-9:40 **Single Cell-Based Digital Twins for Precision Medicine**
Mikael Benson (Swedish Digital Twin Consortium, Linkoping University/ Karolinska Institute Sweden)

9:40-10:00 **Open Discussion**

Session IV: The Exposome
Co-Moderators: Yang-Yu Liu and Mohit Jain

10:00-10:20 **Omics Analysis of the Environmental Determinants of Cardiovascular Disease**
Aruni Bhatnagar (University of Louisville)

10:20-10:40 **Networks and the Microbiome**
Yang-Yu Liu (Brigham/Harvard)

10:40-11:00 **High-Throughput Metabolomics, the Exposome, and Disease Risk**
Mohit Jain (UCSD)

11:00-11:20 **Cheminformatics and the Exposome in Health and Disease**
Emma Schymanski (University of Luxembourg)

11:20-11:35 **Open Discussion**

Session V: Machine Learning/Artificial Intelligence in Network Medicine
Co-Moderators: Jane Leopold and Jan Baumbach

11:35-11:55 **High Performance Computing and Real-time Coronary Pathophysiological Analysis**
Jane Leopold (Brigham/Harvard)

11:55-12:15 **Characterization of the Oxidative Stress-Sensitive Posttranslational Modification Landscape in Mouse Models and Human Heart Failure**
Peipei Ping (UCLA)

12:15-12:35 **Data Privacy in Network Medicine**
Jan Baumbach, (University of Hamburg, Germany)

12:35-12:50 **Open Discussion**

12:50-1:50 **Lunch Break**

Session VI: Practical Applications to Disease
Co-Moderators: Paolo Parini and Edwin K. Silverman

1:50-2:10 **Network Medicine Approach to Atherosclerosis**
Paolo Parini (Karolinska University, Sweden)

2:10-2:30 **Mechanism-based Redefinition of Retinopathy Endophenotypes**
Christina Kiel (University College Dublin, Ireland)

2:30-2:50 **miRNA Interactome Network in Cardioprotection and Cardiotoxicity**
Peter Ferdinandy (Semmelweis University/Pharmahungary Group, Hungary)

2:50-3:15 Break

3:15-3:30 **Network Medicine and Pulmonary Hypertension**
Stephen Chan (University of Pittsburgh)

3:30-3:50 **Molecular Networks in IPF**
Naftali Kaminski (Yale)

3:50-4:10 **Network-based Insights into COPD**
Edwin K. Silverman (Brigham/Harvard)

4:10-4:30 **Big Cancer Data in Cancer Systems Medicine**
Sona Vasudevan (Georgetown University)

4:30-5:00 **Open Discussion**
Debrief and Q & A
Closing

Speaker Abstracts

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Interactome Variants, Personalized Reticulotypes, and Precision Medicine

The fundamental principle of network medicine is based on the identification and characterization of (macro)molecular interaction networks. These networks are analyzed statically and dynamically, and variations within them can be used to characterize functional consequences for disease susceptibility or expression. In recent work, we showed that genetic variants associated with disease, both germline and somatic, are significantly enriched in sequences encoding protein-protein interaction interfaces compared to variants not associated with disease. We experimentally validated the functional consequences of these disease-causing interface mutations on binary interaction assays as well as cell growth assays. These observations lent support for our work on exploring the network basis for different manifestations of the same disease within a cohort of patients with that disease. Here, we developed the concept of individualized protein-protein interaction networks, or unique 'reticulotypes,' that reflect differential gene (and protein) expression in a target organ with the phenotype of interest. Using myectomy specimens from hypertrophic cardiomyopathy patients, we found that the reticulotypes were quite variable in complexity and enriched for thirty endophenotypes. Select endophenotypes were associated with distinct cardiac phenotypes, and also suggested unique drug targets that could be used for precision therapeutics. Thus, patient-specific reticulotypes may serve as the basis for characterizing the pathobiology of a disease phenotype in an individual patient, for identifying specific pathway or protein targets for drug development, for constructing unique biomarkers for disease prognosis, and for repurposing approved drugs whose targets may be proximal to the disease sub-network of interest. In these ways, network medicine offers a truly novel path toward (re)defining and treating human disease in the modern era, and facilitates the trajectory of true precision medicine.

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Why Bother With Networks?

As biologists, we often think of the expression of particular genes as biomarkers for a specific phenotype or disease state and look for patterns of expression to as predictors of endpoints such as response to therapies. However, as network scientists, we recognize that the patterns of expression we observe are the product of complex, multifactorial networks that control when and how

particular genes are activated or deactivated. These networks not only determine the current state of a cell, but also help to control the ways in which cells can respond to perturbations. Not only that, but networks present an environment in which emergent properties can arise as new functional subnetworks are created through the creation of destruction of small numbers of network edges. As we have explored a broad range of biological systems, we have found that networks provide a unique perspective on the biological drivers of phenotypes, revealing features that provide insight beyond what we see with expression, or any other genomic data type alone.

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Ontological and Connectivity Structure of Disease-Gene Modules in the Human Interactome
(Giorgio Grani, Lorenzo Madeddu and Paola Velardi)

Objective:Human-curated disease ontologies are widely used for diagnostic evaluation, treatment and data comparisons over time, and clinical decision support. The classification principles underlying these ontologies are guided by the analysis of observable pathological similarities between disorders, often based on anatomicalor histological principles. Although, thanks to recent advances in molecular biology, disease ontologies are slowly changing to integrate the etiological and genetic origins of diseases, nosology still reflects this "reductionist" perspective. Proximity relationships of disease modules (hereafter DMs) in the human interactome network are now increasingly used in diagnostics, to identify pathobiologically similar diseases and to support drug repurposing and discovery. On the other hand, similarity relations induced from structural proximity of DMs also have several limitations, such as incomplete knowledge of disease-gene relationships and reliability of clinical trials to assess their validity. The purpose of the study described in this paper is to shed more light on disease similarities by analyzing the relationship between categorical proximity of diseases in human-curated ontologies and structural proximity of the related DM in the interactome.
Method: We propose a methodology (and related algorithms) to automatically induce a hierarchical structure from proximity relations between DMs, and to compare this structure with a human-curated disease taxonomy.
Results: We demonstrate that the proposed methodology allows to systematically analyze commonalities and differences among structural and categorical similarity of human diseases, help refine and extend human disease classification systems, and identify promising network areas where new disease-gene interactions can be discovered.

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Cells, Tissues, and Regulatory Networks

Although all human cells carry out common processes, they also have distinct regulatory programs that control specific functions. By modelling a cell's gene regulatory network, we can gain important insights into the underlying molecular mechanisms influencing cellular state. Over the past years, we have developed a suite of methods to effectively integrate multi-Omic data, reconstruct gene regulatory networks, and associate specific regulatory relationships with cellular phenotype. The basis of this work includes PANDA (Passing Attributes between Networks for Data Assimilation), a method that constructs directed genome-wide regulatory networks by using a "message passing" approach to integrate multiple types of genomic data, as well as LIONESS, a method that estimates sample-specific networks by comparing two aggregate network models. We have applied these tools to gain mechanistic insights into many biological systems, including to study tissue-specific regulatory processes and sexual differences in thirty-eight tissues profiled in the Genotype-Tissue Expression (GTEx) project. In this analysis, we found that, although the regulation of tissue-specific function is largely independent of transcription factor expression, tissue-specific genes assume bottleneck positions in their corresponding tissue-network. In addition, sex-biased network targeting was enriched for tissue- and disease-related functions, but independent of gene differential expression. These results suggest that both tissue-specificity and sex differences involve context-specific regulatory paths. We are now working on expanding our methods to integrate additional sources of data such as micro-RNA regulatory relationships and epigenetic information. Together these methods provide a broad-based platform with which to integrate multi-Omics data, infer regulatory networks, and to interrogate those networks to understand alterations in biological processes across heterogeneous populations.

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Biochemical networks of redox biology

Living organisms use redox reactions to extract energy from foods and O_2, maintain bioenergetics and metabolism, support macromolecular organization and function, defend against external threats, and support reproduction. The redox code is a set of principles describing the organization of redox networks to support these key functions. The most general characteristic is that internal environments are maintained under more reduced conditions than external environments, which commonly have higher O_2 and are relatively oxidizing. Organization in cells and subcellular compartments occurs through central redox hubs dependent upon NADH/NAD^+, O_2, NADPH/$NADP^+$, and H_2O_2. The NADH/NAD^+ and O_2 hubs are most central in catabolic processes to maintain forms of energy for work while the NADPH/$NADP^+$ and H_2O_2 hubs serve three major functions, anabolism, defense against external threats, and maintenance of macromolecular

organization and function through reversible sulfur switches in proteins. Cysteine (Cys) residues in proteins are the most common redox switches, and these are controlled by thiol/disulfide hubs [thioredoxins (Reduced/Oxidized), glutathione (GSH/GSSG), cysteine (Cys/CySS)]. The redox switching mechanisms include nitrosylation and glutathionylation; these control enzyme catalytic activities, receptor binding, protein-protein-nucleic acid interactions and other critical aspects of macromolecular structure and function. The NADH/NAD^+ and O_2 hubs also support switching mechanisms for structure and function of protein networks through phosphorylation, acetylation, methylation, and other modifications. Model systems research provides considerable detail for these networks, and integrative omics has revealed antagonistic pleiotropy in redox signaling and control. Importantly, translation of these redox network concepts to human pathophysiology has begun to occur through research showing that plasma GSH and cysteine redox couples are closely linked to metabolic pathways in tissues. In humans, plasma GSH and cysteine systems vary with aging, obesity, type 2 diabetes, diet, environmental exposures, cigarette smoking and alcohol abuse. Importantly, plasma GSH and cystine (CySS) are independent predictors of all-cause mortality in coronary artery disease patients. The results provide hope that central redox measures such as plasma GSH and CySS can be developed to monitor function of central redox networks and facilitate new opportunities for redox medicine.

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Visualizing Networks: VRNetzer — A Virtual Reality platform for exploring complex networks

Networks provide a powerful representation of complex systems of interacting components. In addition to a wide range of available analytical and computational tools, networks also offer a visual interface for exploring large data in a uniquely intuitive fashion. However, the size and complexity of many networks render static visualizations on common screen or paper sizes impractical and result in proverbial 'hairballs'. Here, we introduce an immersive Virtual Reality (VR) platform that overcomes these limitations and unlocks the full potential of visual, interactive exploration of large networks. Our platform is designed towards maximal customization and extendibility, with key features including import of custom code for data analysis, easy integration of external databases, and design of arbitrary user interface elements. Our platform represents a first-of-its-kind, general purpose VR data exploration platform in which human intuition can work seamlessly together with state-of-the-art analysis methods for large and diverse data.

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The Dark Matter of Nutrition: From the Foodome to Network Medicine

Our understanding of how diet affects our health is limited to the role of 150 key nutritional components systematically tracked by the USDA and other national databases in all foods. Yet, these nutritional components represent only a tiny fraction of the over 26,000 distinct, definable biochemicals present in our food. While many of these biochemicals have documented effects on health, they remain unquantified in any systematic fashion across different individual foods. Their invisibility to experimental, clinical, and epidemiological studies defines them as the 'Dark Matter of Nutrition.' I will speak about our efforts to develop a high-resolution library of this nutritional dark matter, and the tole of network medicine in our journey to uncover the role of individual food molecules in our health, opening up novel avenues by which to understand, avoid, and control disease.

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Predicting signed interactions, including drug combinations and genetic interactions

We are witnessing an unprecedented boom in biological data availability, inevitably leading to a turning point, where theory can be a guiding force behind experimental design and development, similarly to what happened in physics. Molecules in our cells, genes in our genome or individuals in our societies do not serve their functions in isolation, but in concert with other nodes in their networks, as well as with environmental factors. Pairwise interactions and correlations are an important starting point, captured by signed network models. Yet, a sufficient understanding of cancer and complex diseases, as well as drug combinations or genetic interactions requires to consider interactions of higher order, between multiple nodes and conditions. Hindered by a combinatorial explosion, limited data availability and quality, going beyond second order in a data-driven way is extremely demanding, with only a handful of examples. In the talk, I will show how to fight data incompleteness and biases with novel methods, leading to experimentally testable, large-scale predictions. Besides bio-physical interactions, our approach can reliably predict a broad spectrum of functional associations, including disease associations, pathway membership and genetic interactions, as well as toxic and synergistic drug combinations. I will close by highlighting future research directions.

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Orthogonal Phenotyping and Disease Definition

The focus of most human disease analyses is a series of largely legacy disease definitions or phenotypes, many of which originated in organ specific anatomic pathology or physiology. While these have served biomedicine well, the underlying etiologic heterogeneity, the absence of clear pathophysiologic or prognostic boundaries between sub-phenotypes and the general lack of information content in these phenotypes is increasingly recognized as a barrier to progress. Genetic analyses of causation are confounded by unresolved primary mechanisms, animal modeling is confined to analogy and the vast majority of therapeutic development programs fail. To overcome these fundamental barriers to progress, the empiric discovery of novel discriminant human phenotypes will be necessary. This nominally unbiased discovery of 'orthogonal' information content is a requirement for effective deep phenotyping and can be imagined as a series of iterative strategies generating novel phenotypes with specific properties. These novel phenotypes might ideally be highly scalable, clinically relevant, dynamic with linear response characteristics over several log orders, and directly translatable to animal or cellular models by design. We have undertaken a systematic effort to create such "massively parallel" clinical phenotypes, typically using perturbations to identify latent traits and artificial intelligence to define novel sub-states of health or disease, which can then be selected on the basis of relevance and effect size to ensure a high likelihood of monogenic or oligogenic mechanism for efficient target identification. The utility of such phenotypes with associated revealing perturbations for efficient rapid cycle translation between humans and model systems facilitates mechanistic studies, drug discovery and clinical trials. Ultimately, central goals of our approach are cost-effective, universal genome annotation and redefinition of disease on the basis of mechanism at an individual patient level.

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Identifying the molecules mediating cross-tissue interactions of gene regulatory networks

(Marcus Seldin[1], Simon Koplev[2], Aldons J. Lusis[3] and Johan L.M. Bjorkegren[1])
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Our groups have used Gene Regulatory Networks (GRNs) based on co-expression and prior causal information to understand interactions within a particular cell type as well as interactions between tissues, that is, cross-tissue GRNs. Such cross-tissue interactions are generally mediated by secreted endocrine factors or by the nervous system. We have previously described a bioinformatics approach to identify novel cross-tissue endocrine circuits (Seldin et al. Cell Metab. 27:1138, 2018). This approach uses gene expression data from multiple tissues in a population to identify correlation structure between the expression of a candidate endocrine factor in one tissue and

global gene expression in a second (target) tissue. We now show that the method is useful for establishing cross-tissue edges between GRNs. These studies utilized RNA sequence data for seven disease-relevant tissues from the Stockholm-Tartu Atherosclerosis Reverse Engineering Task (STARNET). Strong cross-tissue interactions were identified along an axis from subcutaneous and abdominal fat to liver and several predicted factors mediating the interactions, including EPDR1, FCN2, FSTL3 and LBP, were validated by injection of the recombinant forms in mice.

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Network Medicine and Personalized Disease Phenotype

Cardiovascular diseases are complex and driven by integrated molecular signaling pathways that underpin heterogeneity in clinical phenotype. This is the case even for many clinical disorders that are described classically as monogenic, thereby introducing unique challenges to individualizing the pathobiology-clinical phenotype relationship in patients. Network medicine is a proven strategy by which to clarify the mechanisms that regulate endophenotypes important in the pathogenesis of cardiovascular disease. Utilizing biological networks in precision medicine, however, requires an innovative approach that leverages patient-specific pathobiological features, focuses on protein-protein interactions (PPIs), and joins in clinical data. This presentation will discuss a contemporary method based on developing patient-specific PPIs that are then used to predict endophenotype and prognostic clinical parameters on the level of an individual patient. This approach illustrates an innovative direction to expand the potential of network medicine for understanding cardiovascular and other complexes diseases, focusing specifically on forward-thinking strategies that advance precision medicine.

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Network-based Approaches for the Identification of Cancer Signatures from Omics Data

Integrating the outcomes of co-expression network analysis with the human interactome network could aid to predict novel putative disease genes and modules. Recently, SWItch Miner (SWIM) methodology, which predicts important (switch) genes within the co-expression network that regulate disease state transitions, has been successfully applied to chronic obstructive pulmonary disease (COPD), a severe lung disease characterized by progressive and incompletely reversible

airflow obstruction [1]. COPD switch genes appear to form localized connected subnetworks displaying an intriguingly common pattern of upregulation in COPD cases compared with controls. A more sophisticated analysis revealed that they were not only topologically related, but also functionally relevant to the observed phenotype as witnessed by their enrichment in the regulation of inflammatory and immune responses. The results obtained in COPD were compared with those obtained in the acute respiratory distress syndrome (ARDS), another severe lung disease with an inflammatory component. Interestingly, ARDS switch genes were different from COPD switch genes, but the major pathways affected in the two diseases were similar, emphasizing that different diseases often have common underlying mechanisms and share intermediate endophenotypes (convergent phenotypes) [2,3]. Moreover, the two lists of switch genes, when mapped to the human interactome, appear to form non-overlapping modules and to be situated in different network neighborhoods. This observation demonstrates that even though different diseases can share similar endophenotypes, the molecular network determinants responsible for them are disease-specific. Inspired by the results obtained by SWIM network analysis of cancers and COPD[1,4], we investigated three other complex diseases for a more generalizable understanding of the highly interconnected nature of human diseases. Specifically, two cardiac disorders, ischemic and non-ischemic cardiomyopathy, and one neurodegenerative disorder, Alzheimer's disease, were analyzed. These new results, together with the previously obtained analyses from the application of SWIM to ten different tumor types and COPD, were mapped to the human interactome in order to overlay the PPI network with disease information derived from SWIM-based disease correlation networks. Our goal was to assess the utility of SWIM network analysis in classifying several different disorders and in understanding their complex interconnections in the human interactome. In particular, through the construction of a SWIM-informed human disease network by analogy with [5], we found that switch genes associated with specific disorders are closer to each other than to other nodes in the network, and tend to form localized connected subnetworks. These subnetworks overlap between similar diseases and are situated in different neighborhoods for pathologically distinct phenotypes, consistent with the well-known topological proximity property of disease genes. These findings allowed us to demonstrate how SWIM-based correlation network analysis can serve as a useful tool for efficient screening of potentially new disease gene associations. When integrated with an interactome-based network analysis, it not only identifies novel candidate disease genes, but also may offer testable hypotheses by which to elucidate the molecular underpinnings of human disease and reveal commonalities between seemingly unrelated diseases.

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Big Data and the Comorbidity Landscape

Network science and machine learning to understand disease have been largely championed by distinct research communities. This is particularly evident in analyses of the comorbidity landscape of ostensible disease categories that are in reality constellations of distinct pathophysiologies with overlapping manifestations. I'll illustrate this with examples drawn from our research in autism. I'll conclude with recent developments in machine learning that embrace some of the important axioms of network science.

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Longitudinal Phenotypes and Disease Trajectories at Population Scale

Multi-step disease and prescription trajectories are key to the understanding of human disease progression patterns and their underlying molecular level etiologies. The number of human protein coding genes is small, and many genes are presumably impacting more than one disease, a fact that complicates the process of identifying actionable variation for use in precision medicine efforts. We present approaches to the identification of frequent disease and prescription trajectories from population-wide healthcare data comprising millions of patients and corresponding strategies for linking disease co-occurrences to genomic individuality. We carry out temporal analysis of clinical data in a life-course oriented fashion. We use data covering 7-10 million patients from Denmark collected over a 20-40 year period and use them to "condense" millions of individual trajectories into a smaller set of recurrent ones. Such sets represent patient subgroups sharing longitudinal phenotypes that could form a basis for differential treatment designs of relevance to individual patients.

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Quantitative Phenotype Imaging

Advanced medical imaging technology such as computed tomography became widely available in the 1990s and afforded clinicians high resolution in-vivo data from which they could understand organ structure and dysfunction. As image processing progressed, subjective bedside interpretations were augmented with objective techniques that could segment structures of interest and extract features useful for disease detection, stratification and prognostication. These advances supported an almost universally held belief that imaging would rapidly propel precision medicine. Almost 3 decades have since elapsed, and the biomedical community has yet to realize imaging's full potential. This is not for a lack of computational capacity or limits to image resolution, but rather the complexity of disease and a growing appreciation of the simplicity of our disease definitions. Chronic disease is an accrual of a lifetime's exposure which in a susceptible individual manifests as a clinically recognizable condition we label as COPD or cardiovascular disease. Susceptibility is more than an acute biological response to a noxious exposure. It includes factors such as innate organ structure and functional reserve at peak organ health. Imaging is teaching us about the heterogeneity of disease and is increasingly informing our understanding of organ structure in ideal health. Optimal use of imaging in chronic disease must include enhanced precision of longitudinal assessments as well as the exploration of under-recognized comorbidities that may be highly clinically relevant and more dynamic than summary measures of organ function such as spirometry or ventricular ejection fraction. Finally, as we translate research-based approaches to image analysis into clinically acquired data we must not underestimate the burden of data cleaning necessary to facilitate this process. We also cannot underestimate the risk of training our biases in clinical care into machine learning algorithms that we assume to be free of discrimination.

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Brain Network Topology Maps the Dysfunctional Substrate of Cognitive Processes in Schizophrenia

(Rossana Mastrandrea, Fabrizio Piras, Andrea Gabrielli, Guido Caldarelli, Gianfranco Spalletta, Tommaso Gili)

Using a novel network analysis of spontaneous low-frequency functional MRI data recorded at rest, we study the functional network that describes the extent of synchronization among different areas of the brain. Comparing forty-four medicated patients and forty healthy subjects, we detected significant differences in the robustness of these functional networks. Such differences resulted in a larger resistance to edge removal (disconnection) in the graph of schizophrenic patients as compared to healthy controls. This paper shows that the distribution of connectivity strength

among brain regions is spatially more homogeneous in schizophrenic patients with respect to healthy ones. As a consequence, the precise hierarchical modularity of healthy brains is crumbled in schizophrenic ones, making possible a peculiar arrangement of region-to-region interaction that, in turns, produces several topologically equivalent backbones of the whole functional brain network. We hypothesize that the manifold nature of the basal scheme of functional organization within the brain, together with its altered hierarchical modularity, contributes to positive symptoms of schizophrenia. Our work also fits the disconnection hypothesis that describes schizophrenia as a brain disorder, characterized by abnormal functional integration among brain regions

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Predicting drug response and synergy using deep learning models of human cancer

Most drugs entering clinical trials fail, often related to an incomplete understanding of the mechanisms governing drug response. Machine learning techniques hold immense promise for better drug response predictions, but most have not reached clinical practice due to their lack of interpretability and their focus on monotherapies. To address these challenges, I will describe development of DrugCell, an interpretable deep learning model of human cancer cells trained on the responses of thousands of tumor cell lines to thousands of approved or exploratory therapeutic agents. The structure of the model is built from a knowledgebase of molecular pathways important for cancer, which can be drawn from literature or formulated directly from integration of data from genomics, proteomics and imaging. Based on this structure, alterations to the tumor genome induce states on specific pathways, which combine with drug structure to yield a predicted response to therapy. The key pathways in capturing a drug response lead directly to design of synergistic drug combinations, which we validate systematically by combinatorial CRISPR, drug-drug screening in vitro, and patient-derived xenografts. We also explore a recently developed technique, few-shot machine learning, for training versatile neural network models in cell lines that can be tuned to new contexts using few additional samples. The models quickly adapt when switching among different tissue types and in moving to clinical contexts, including patient-derived xenografts and clinical samples. These results begin to outline a blueprint for constructing interpretable AI systems for predictive medicine.

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Network Pharmacology: From Chronic Disease to Mechanism-Based Cure

For complex diseases, most drugs are highly ineffective, and the success rate of drug discovery is in a constant decline. Whilst low quality, reproducibility issues, and translational irrelevance of most basic and preclinical research have contributed to this, the current organ-centricity of medicine and the one disease-one target-one drug dogma obstruct innovation most profoundly. Systems and network medicine and their therapeutic arm, network pharmacology, revolutionize how we define, diagnose, treat and ideally cure diseases. Descriptive disease phenotypes are replaced by endotypes defined by causal, multi-target signaling modules that also explain respective comorbidities. These modules are however distinct from classical pathways, which we now recognize to be not more than highly curated mind maps of signaling events. Modules more often than not contain several fragments of several different canonical pathways. Precise and effective therapeutic intervention depends on precise inclusion and exclusion of module members and is subsequently achieved by synergistic multi-compound network pharmacology, ideally through drug repurposing, obviating the need for drug discovery, and speeding up the clinical translation. Network pharmacology is, however, not to be confused with current combination therapies with multiple non-synergistic drugs targeting non-causal proteins that rather treat symptoms but do not cure disease.

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Systems Pharmacology for drug target identification and repurposing

(Ravi Iyengar, Jens Hansen and Francesco Ramirez)

The development of computational models of cell-based pathways underlying whole cell functional from transcriptional profiling offer a powerful approach to identify new targets for complex progressive diseases and for repurposing FDA approved drugs. Thoracic aortic aneurysms and dissections are life-threatening degenerative diseases often associated with genetically triggered defects such as in Marfan syndrome result in major structural and instructional determinants of aortic tissue integrity and homeostasis. Currently there are no drugs to treat aneurysms.

We used computational modeling of transcriptomic data to predict protein kinases that may be responsible for dysregulated gene expression in vessel walls with aneurysms from patients and mice with progressively severe Marfan syndrome (MFS). Homeodomain-interacting protein kinase 2 (HIPK2) was identified as the top ranked aneurysm related protein kinase in both human and mouse samples. In agreement with our computational prediction, HIPK2 was upregulated in the aorta of Marfan mice along with greater phosphorylation of two putative target transcriptional regulators Smad2 and p53. Ubiquitous post-natal inactivation of the Hipk2 gene extended the median survival of Marfan mice by mitigating the aneurysm pathology and delaying the occurrence of aortic dissections. Chronic administration of an allosteric inhibitor of HIPK2/Smad2 interaction (compound BT173) to Marfan mouse pups significantly improved median survival associated with substantially mitigated aneurysm histopathology and improved aortic tissue compliance suggesting that new drugs that target HIPK2 may be used to treat aneurysms.

We have also used transcriptomic data to identify current FDA approved drugs that could be repurposed to treat aneurysms. For this, we computationally analyzed transcriptomic data derived from the aortas of Marfan syndrome patients and mice and identified subcellular pathways associated with reduced muscle contractility as key determinants of aneurysms. We then used these pathways to search the CMAP database to identify drugs that affect expression of components of these and associated pathways. Using this approach, we identified the GABA-B receptor agonist baclofen a drug commonly used to treat spastic disorders as a potential drug to treat aneurysms. Systemic administration of baclofen to Marfan syndrome mice validated our computational prediction by mitigating arterial disease progression at the cellular and physiological levels. Interestingly, baclofen improved muscle contraction–related subcellular pathways by upregulating a different set of genes than those downregulated in the aorta of vehicle-treated Marfan mice. The transcriptomic profiles of drug-treated Marfan syndrome mice was also different from that of wild-type mice suggesting that there may be multiple modalities to obtain normal aortic physiology.

Overall, our studies show that systems pharmacology approaches could be effective in using cell-based pathways and processes in identifying drugs to treat progressive diseases.

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High Performance Computing and Unbiased Drug-Target Identification

As the world was faced with the COVID-19 pandemic, people raced to develop new vaccines and therapeutics to combat SAR-CoV-2. In our efforts, we focused on developing and utilizing high performance computing methods to speed up the discovery and design of inhibitors to two SARS-CoV-2 proteins, spike and main protease (Mpro). While screening for small molecule hits, a number of methods were developed, used, and validated to improve predictions of small molecule binding to proteins at scale, including molecular docking, a 3-D structure-based deep learning model, MM/GBSA free energy calculations, neural network GBSA score predictors, and molecular dynamics simulations. Molecular docking screened 1.64 billion compounds for each of the four identified binding pockets and was used as a first pass filter for the subsequent methods. Two 3-D structure-based deep learning models seem to improve rescoring of the docked poses, as well as MM/GBSA free energy calculations. Over a thousand compounds were purchased and tested by using in-vitro assays for binding to spike protein, inhibition of MPro function and cell infection by spike-expressing pseudovirus. Compounds that inhibited the pseudovirus were further tested against live SARS-CoV-2 virus. Of the screening methods used here, the best predictor of experimental results is MM/GBSA free energy; however, MM/GBSA scores computed by neural network models from chemical descriptor features do almost as well. Our results, including 26M small molecules, proteins and co-complexes, are a total of 10TB of data files and are available through a dataportal. The estimate for the total set of results is 180TB of data. Having tested and validated our methods to predict small molecule binding, we plan use these same tools to predict small molecule binders to approximately 9000 human proteins. Prepared by LLNL under Contract DE-AC52-07NA27344.

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Harnessing Network Medicine and Endophenotypes for Alzheimer's Drug Repurposing

There is an urgent need for effective therapeutic treatments for patients with Alzheimer's disease (AD). We posited that systematic identification of underlying AD-related endophenotype molecular network modules, shared by amyloidosis and tauopathy, would provide a foundation for generating predictive models to characterize AD pathogenesis for efficacious therapeutic development. To address this need, we developed an endophenotype disease module-based methodology for AD drug repurposing and then validated network-based predictions using state of-the-art pharmacoepidemiologic analysis of 7.23 million U.S. commercially insured individuals (MarketScan Medicare supplementary database). We found that network-predicted sildenafil usage was significantly associated with a 69% reduced risk of AD, compared with matched non-sildenafil users (hazard ratio [HR] =0.31, 95% confidence interval [CI] 0.25-0.39, $P < 1 \times 10^{-8}$). In addition, sildenafil usage was significantly associated with reduced likelihood of AD across all five drug cohorts in individuals with coronary artery disease (CAD), hypertension (HT), and type 2 diabetes (T2D), and in individuals after excluding CAD, HT, and T2D as well. Age-specific subgroup analyses showed that sildenafil was significantly associated with reduced likelihood of AD across all five drug cohorts in both mid-older (65-74 years) and older individuals (75-100 years). Finally, *in vitro* experiments show that sildenafil downregulates GSK3β and CDK5 in human microglia cells, supporting a possible mechanism for its beneficial effect in AD. In summary, this talk will discuss a proof-of-concept of endophenotype network-based drug discovery and identifies that sildenafil is a promising drug candidate for potential prevention and treatment of AD.

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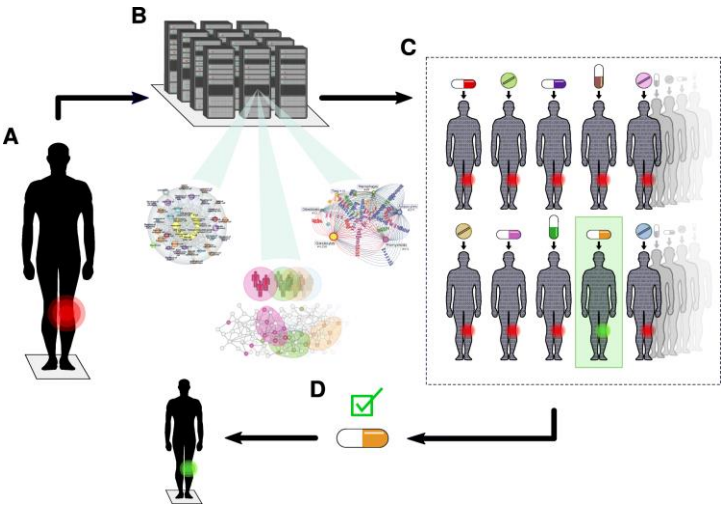
Single cell-based digital twins to personalize medicine

One of the greatest health care problems is that a large number of patients do not respond to drug treatment. An important reason is the complexity of common diseases, which may involve altered interactions between thousands of genes, across multiple cell types and tissues. The Swedish Digital Twin Consortium aims to address this by constructing digital twins of individual patients. The twins are genome- and cellulome-wide network models of single cell data from the patients. Network tools are applied to computationally treat each twin with thousands of drugs in order to find the optimal drug for each patient (figure 1).



The concept has been validated by therapeutic mouse model studies, and is now tested in clinical studies (all references are found on our website: sdtc.se).

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Omics Analysis of the Environmental Determinants of Cardiovascular Disease

Extensive evidence suggests that a majority of cardiovascular disease originates from adverse environmental conditions and exposures. Nevertheless, in contrast to genetic factors, environmental determinants of cardiovascular disease have received less attention, and there is no systematic framework for studying the role of environmental factors in maintaining or diminishing cardiovascular health. However, the concept of the "envirome" (analogous to the genome) provides new opportunities for evaluating and estimating the collective health impact of the natural, social, and personal domains of the environment. This, categorically-differentiated, domain-specific model of the general environment as an individual envirome could be useful in identifying the ontology of environmental factors (akin to gene ontologies), and in studying environmental influence on cardiovascular health. By adopting an omics approach, the model creates a basic framework for understanding and explaining how ecological and social factors interact with each other, and how they collectively and individually affect cardiovascular disease risk. The model could be a blueprint - not only for studying the effects of natural factors, such as sunlight, diurnal cycles, seasons, and geography on cardiovascular health, - but also for assessing how the influence of the natural environment is moderated by features of the social environment, such as pollution, socioeconomic status, civic policies, and the built environment. Importantly, the model could aid in isolating, understanding, and evaluating the effects of the natural and the social environments on the characteristics of the personal environment, which includes nutrition, sleep, smoking, chemical use, occupation, income, and education. Hence, studying the architecture of individual enviromes with the help of recently-developed tools for monitoring and analyzing the natural, social, and personal domains of the environments could lead to a better understanding of the non-biological etiology of

cardiovascular disease, and how the disease could be managed or prevented more effectively in the future.

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Networks and the Microbiome

We coexist with a vast number of microbes that live in and on our bodies. Those microbes and their genes are collectively known as the human microbiome, which plays important roles in human physiology and diseases. Many scientific advances have been made through the work of large-scale, consortium-driven metagenomic projects, which help us acquire more accurate organismal compositions and metabolic functions of the human microbiome. Yet, unfortunately, FDA has not approved any microbiome-based therapeutics so far! I consider there are many several fundamental challenges down the road. First, our microbiome is highly personalized. Second, we don't know its wiring diagram. Third, our microbiome is very stable and resilient to small perturbations! In this talk, I will present our recent progress on understanding this complex ecosystem using network approaches. In particular, I will address the following key questions: Do our microbiome share similar microbial dynamics or ecological network, despite the highly personalized microbial compositions? How to map the ecological network of our microbiome and leverage the network to design personalized microbiome-based therapeutics? What's the origin of the stability and resilience of our microbiome?

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High-Throughput Metabolomics, the Exposome, and Disease Risk

Human health and disease are the manifestation of environmental exposures superimposed on underlying genetic predisposition. Whereas genetic factors are largely unchanged from conception, environmental exposures are dynamic and cumulative over the lifespan, ultimately accounting for the majority of population-attributable risk for common human disease. The totality of environmental exposures, or the 'exposome', represents the aggregate of both *internal* exposures originating from host state/physiology and host microbiota, as well as *external* exposures including toxicants, infectious agents, diet and drugs. These environmental exposures result in the introduction of small molecule metabolites into human circulation that may be monitored as biomarkers or *functional surrogates* of the exposome, even years or decades prior to onset of disease. As part of this Second International Conference on Network Medicine and Big Data, we will

provide an overview of our strategies to utilize high throughput mass spectrometry to (i) map the thousands of molecules that comprise the human exposome across 50,000 diverse individuals from around the world, (ii) identify the components of the exposome attributable to specific environmental exposures, and (iii) determine the role of the exposome in mediating human disease.

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Cheminformatics and the Exposome in Health and Disease

The exposome "strives to capture the diversity and range of exposures to synthetic chemicals, dietary constituents, psychosocial stressors, and physical factors, as well as their corresponding biological responses" [1] over an entire lifetime. Alone the environment and the chemicals to which we are exposed is incredibly complex, with over 100 million chemicals in the largest open chemical databases and over 70,000 in household use alone. Detectable molecules in exposomics can now be captured using high resolution mass spectrometry (HRMS), which provides a "snapshot" of all chemicals present in a sample and allows for retrospective data analysis through digital archiving. However, there is no "one size fits all" analytical method, and scientists cannot yet identify most of the tens of thousands of features in each sample, let alone associate them with health or disease, leading to critical bottlenecks in identification and data interpretation. Defining the chemical space to search, the analytical methods to use, prioritizing efforts to find significant environmental chemicals, metabolites or biomarkers will be the key to the exposomics challenge, which involves reconciling highly complex samples with expert knowledge and careful validation. This talk will cover European and worldwide community initiatives and resources to help connect knowledge on exposomics - from compound databases to spectral libraries and retrospective screening and will show how interdisciplinary efforts and data sharing can facilitate research in exposomics and beyond. Various contributors to this massive collaborative effort will be acknowledged throughout the talk.

[1] Vermeulen, R. *et al*. 2020. The exposome and health: Where chemistry meets biology. Science 367:392. DOI: 10.1126/science.aay3164

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High Performance Computing and Real-time Coronary Pathophysiological Analysis

Cardiovascular disease is the leading cause of death worldwide with 4 out of 5 deaths attributable to myocardial infarction or stroke. Patients with symptomatic disease are referred for an invasive

diagnostic coronary angiogram to create a map of the coronary arteries and identify blockages. This is often coupled with a therapeutic procedure, a percutaneous coronary intervention (PCI) with stent implantation, to alleviate the blockage or a referral for cardiac surgery. The decision to perform a PCI is dependent upon demonstrating ischemia (restriction in blood flow leading to a decrease in oxygen) in the cardiac muscle territory supplied by the artery. Current practice is to assess ischemia at the time of the coronary angiogram by performing a pressure measurement across a blockage using a wire with a pressure sensor: ischemia is present if the distal-to-proximal pressure ratio is ≤ 0.8. The wire-based measurement, however, adds time, cost, and increased risk to the overall procedure. Furthermore, stent implantation, while effective at reducing symptoms, also has limitations. Stents can become blocked due to excess tissue growth in the lumen of the stent (in-stent restenosis), which occurs in up to 10% of drug-eluting stents. Stents can also be occluded by thrombus (stent thrombosis) although this occurs far less frequently. The underlying causes of these adverse events are incompletely characterized, but procedural characteristics, such as changes in vessel topology, material properties, and local hemodynamics have emerged as significant contributors. Noninvasive strategies that can determine if a stent is required with high accuracy and direct a stenting procedure (type, length, and site of implantation), have the potential to mitigate short- and long-term risk and change process for patients. Utilizing fluid dynamics simulations with virtual stent implantation and high-performance computing, we have developed a pipeline that enables onboard vessel-, and lesion-specific analyses of intravascular hemodynamics (velocity, pressure, shear stress, and vorticity) derived from patient coronary angiograms. Simulations can be performed down to a resolution of 9 μm, which is well below the size of a single stent strut (50 μm). Results can be used to determine if PCI is warranted or to optimize stent implantation procedures and, thereby, decrease risk to patients from additional invasive procedures or to prognosticate adverse outcomes. This pipeline is also applicable to examine the cerebral, pulmonary, and peripheral vascular circulations.

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Characterization of the Oxidative Stress-Sensitive Posttranslational Modification Landscape in Mouse Models and Human Heart Failure

Background: Oxidative stress is a common pathological stimulus contributing to cardiac disease, yet our understanding of oxidative stress-induced protein targets, molecular signaling, functional consequences, and temporal sequencing remain elusive. This is largely due to the complex nature of oxidative stress-induced post-translational modification (O-PTMs) of proteins as well as computational challenges inherent in decoding them. Recently, machine learning (ML) approaches have provided unprecedented power for unveiling complex patterns inherent to large biological datasets. We applied ML approaches to elucidate O-PTM signatures representing cardiac pathology to address its data nature of temporal pattern and high dimensionality.

Methods: Longitudinal datasets over a 14-day duration were generated from mixed murine strains with variable oxidative stress susceptibility. Mouse model of cardiac dysfunction was generated using isoproterenol (ISO) infusion. Myocardial oxidative stress; cardiac function (echocardiography) and O-PTM proteomic features (LC-MS/MS) were characterized. Functional phenotyping ensued via quantifying 15 chemically-distinct O-PTMs (4 sulfur oxidations, 3 carbonylations, and 8 hydroxylations). A novel ML-based platform was developed to link O-PTM fingerprints with cardiac pathological progression. Molecular signatures of cardiac phenotypes were extracted using feature selection algorithms; temporal dynamics were elucidated using cubic spline-based clustering. Unique molecular signatures of disease were validated using three independent mechanisms: (i) computational via model-agnostic interpretability, (ii) biological using in vivo methionine oxidation datasets, and (iii) translational through validation in human heart failure datasets.

Summary: Cardiac pathological remodeling potentiated O-PTMs at 20,237 modified amino acid sites on 2,328 murine cardiac proteins. ML analysis extracted 12 unique O-PTM signatures robustly representing a cardiac pathological phenotype; known hypertrophic pathways such as ETC, cardiac muscle contraction, and inflammation response showed enrichment. Importantly, O-PTM combinations in calcium regulation, fatty acid beta-oxidation, platelet activation, and branched chain amino acid catabolism (BCAA) pathways exhibited distinct temporal profiles, discovering novel molecular signatures that define different phases of cardiac disease progression. Our findings provide the first O-PTM molecular map that serves as an avenue for molecular signature discovery and design of therapeutics.

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Data Privacy in Network Medicine

Artificial intelligence (AI) has been successfully applied in numerous scientific domains. In biomedicine and network medicine, AI has already shown tremendous potential, e.g. in the interpretation of next-generation sequencing data and in the design of clinical decision support systems. However, training an AI model on sensitive data raises concerns about the privacy of individual participants. In genome-wide association studies (GWAS), for example, one may determine the presence or absence of an individual in a given dataset. This considerable privacy risk has led to legal restrictions in accessing genomic and other biomedical data (e.g. the European GDPR), which is detrimental for collaborative research and impedes scientific progress. Hence, there has been a substantial effort to develop AI methods that can learn from sensitive data while protecting individuals' privacy. We introduce FeatureCloud (http://secure-web.cisco.com/199NAX7bBRHAsvlVWOsPlSMiN4HgUk3ojbUZjCWgbbkYX2R0ktEb6JI7tCLPKaG3ryd3IY4TnMbqeo_KetyqKOT_mXfDV0niwwGR_vTtcn-0bodEUERF7q4RWwFla1dXgB7NwrrJGxTzQ7KiKTz3NiPZ9A7YsM9TK86gtq9KLlicK9FInbi2IA7UlF5hVbqPFmy1x46EUCotie85uPKlk9uJiBQrahi_PGHvby5kJbv4-4Je_nbgDf2_39Br75VN1QK9Fwwm2cHgx7ShKci86XA/http%3A%2F%2Ffeaturecloud.ai), an app store for federated statistics and AI tools to overcome this issue by proving privacy-by-design software solutions. We demonstrate the power of federated data mining in practice in GWAS settings, for gene expression-based biomarker profiling, and in different time-to-event analyses schemes.

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Network Medicine Approach to Atherosclerosis

During the last several decades non-communicable diseases (NCDs) have dramatically increased deaths globally. One of themost prevalent NCD, atherosclerotic cardiovascular disease (ASCVD) and cardiometabolic disease (CMD), are now major global health threats and socioeconomic burdens. Combined Hyperlipidemia (CH) is the most common form of hyperlipidemia and impacts longevity by promoting ASCVD, CMD. Conventional 'omics studies, designed to find simple associations between genotype and phenotype in large datasets, are inherently incapable of unraveling the complex pathobiology underlying diseases. Using network analysis, we aim to describe the effects of the peripheral lipoprotein phenotypes of CH described in a multidimensional space by modules of functional interactions, using patients from different existing cohorts to understand whether CH drives accelerated biological ageing, estimated by analysis of the epigenome (DNA-methylation) in conjunction with specific ICD-10 diagnoses and treatments as a function of chronological age. We plan to integrate data of different nature [e.g., genetic, epigenetic, biochemistry, national registries, and electronic health record (EHR), and patient reported outcome measures (PROM) questionnaires]. As initial proof-of-concept, we have created novel multi-source networks in which single-source analyses (i.e., liver transcriptomics and epigenomics) are integrated with biochemical parameters and lipoprotein functionality in combination with Dr. Joseph Loscalzo´s human PPI Personal Protein I. Patients were from the *Stockholm Study*, in non-obese, normolipidemic, gallstone patients (66% female) were randomized to a 4-week treatment with simvastatin 80 mg/day and ezetimibe 10 mg/day, alone or in combination, or to placebo. The first network mining has already indicated a constant and previously unknown interactionbetween a key gene in cholesterol metabolism and TMBIM6, a transmembrane protein involved in autophagy and cancer information contained in the multi-source networks. Validation studies of this initial finding in going on in *Soat2-only* HepG2 cells, a unique pre-clinical model which more closely resembles human lipoprotein metabolism created by us.

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Mechanism-based Redefinition of Retinopathy Endophenotypes
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Retinopathies are a group of monogenetic or complex retinal diseases associated with high unmet medical need. Monogenic disorders are caused by rare genetic variation and usually arise early in life. Other diseases, such as age-related macular degeneration (AMD), develop late in life and are considered to be of complex origin as they develop from a combination of genetic, ageing, environmental and lifestyle risk factors. Here, we contrast the underlying disease networks and pathological mechanisms of monogenic as opposed to complex retinopathies, using AMD as an example of the latter. We show that, surprisingly, genes associated with the different forms of retinopathies in general do not overlap despite their overlapping retinal phenotypes. Further, AMD risk genes participate in multiple networks with interaction partners that link to different ubiquitous pathways affecting general tissue integrity and homeostasis. Thus AMD most likely represents an endophenotype with differing underlying pathogenesis in different subjects. Localizing these pathomechanisms and processes within and across different retinal anatomical compartments provides a novel representation of AMD that may be extended to complex disease in general. This approach may generate improved treatment options that target multiple processes with the aim of restoring tissue homeostasis and maintaining vision.

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MicroRNA Interactome Network in Cardioprotection and Cardiotoxicity

Ischemic heart disease is a leading cause of mortality worldwide, therefore, identification of valid drug targets for cardioprotection is of great importance. The lack of successful translation of cardioprotection to clinical therapy after more than 3 decades of intensive research may include hypothesis driven, biased approach to find molecular targets and the lack of translational experimental models for cardioprotection. Indeed, major cardiovascular comorbidities such as hyperlipidemia (the first comorbidity shown to inhibit the efficacy of ischemic conditioning), diabetes, and their co-medications have been shown to interfere with most of the known cardioprotective mechanisms (see for reviews: Ferdinandy et al, *Pharmacol Rev*, 2007, 2014; Hausenloy et al, *Cardiovasc Res*, 2017). Moreover, comorbidities also may lead to manifestation of hidden cardiotoxicy of drugs (Ferdinandy et al, *Eur Heart J*, 2019; Brenner et al, *Cells*, 2020). Cardioprotection by conditioning and cardiotoxicity have been shown to affect global myocardial gene expression profile showing that cardioprotection and cardiotoxicity trigger a complex network of signaling cascade rather than a single major pathway. Moreover, cardiovascular comorbidities including hypercholesterolemia have been also shown to affect global cardiac gene expression profile at the transcript level including non-coding RNAs like micro-RNAs (Varga et al, *Curr Drug Targets*, 2015; Perrino et al, *Cardiovasc Res*, 2017). MicroRNS are found in all tissues and body fluids carried by extracellular vesicles (Slujiter et al, *Cardiovasc Res*, 2018), therefore, microRNA transcriptomics-based target prediction may be an effective way to find novel molecular targets for cardioprotection by an unbiased way.

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Network Medicine and Pulmonary Hypertension

Pulmonary hypertension (PH) is a mysterious and morbid vascular disease with unclear molecular origins. As a community, we are just beginning to develop the principles of network medicine necessary to translate "big data" to precision practice in PH. Current challenges in data acquisition include tissue source, financial resources, and patient numbers. One example of how network medicine can guide basic and translational understanding in PH is repurposing of therapeutic small molecules from other diseases to PH. Computational drug repurposing is emerging as a viable possibility, given the increasing availability of large-scale clinical and molecular profiling that may be used in combination with emerging network methodologies. However, effective computational screening is lacking, particularly in rare and emerging diseases such as pulmonary hypertension (PH) where statistical power and advanced analytics are often not available across the limited *-omics* datasets of these neglected diseases.

To address this gap in knowledge, via transcriptomic differential dependency analyses leveraging parallels between cancer and PH, we mapped a landscape of cancer drug functions dependent upon rewiring of PH gene clusters across publicly available cancer-related datasets. Bromodomain and extra-terminal motif (BET) protein inhibitors were predicted to rely upon several gene clusters inclusive of galectin-8. Correspondingly, galectin-8 was found to mediate the BET inhibitor-dependent control of endothelial apoptosis, an essential role for PH *in vivo*. Separately, a piperlongumine analog's actions were predicted to depend upon the iron-sulfur biogenesis gene ISCU. Correspondingly, the analog was found to inhibit ISCU glutathionylation, rescuing oxidative metabolism, decreasing endothelial apoptosis, and improving PH. Thus, by coupling computational predictions with extensive experimental validation *in vitro* and *in vivo*, we identified crucial drug-gene axes central to endothelial dysfunction and therapeutic priorities for PH. More broadly, these results establish a wide-ranging, network dependency platform to redefine cancer drugs for use in PH and potentially other non-cancerous conditions.

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Molecular Networks in IPF

Idiopathic Pulmonary fibrosis (IPF) is an incurable disease in which the normal lung anatomy is replaced by a process of active remodeling, and deposition of extracellular matrix (ECM) accompanied by a shift in lung cellular communities. While researchers long acknowledged that fibrosis requires the disruption of organ homeostasis that leads to a permanent shift in its cellular communities and interactions, much of research still focuses on the role of a single pathway in one cell subpopulation. We applied several approaches to better understand the dysregulated cell and gene network that determine the human lung phenotype in IPF. By analyzing differentially affected regions in the human IPF lungs and applying dynamic temporal regulatory networks we identified early and late events in fibrosis. By applying single cell RNA sequencing technologies to >600,000 lung and blood cells from >100 individuals with IPF, as well as other advanced lung disease, we identified the presence of a self-propagating fibrotic niche, in which previously unrecognized aberrant basaloid cells, ectopically present systemic endothelial cells, altered fibroblast and immune cell populations, that replaces that the homoeostatic alveolar niche. The results, as well as their therapeutic implications will be discussed.

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Network-Based Insights into Chronic Obstructive Pulmonary Disease

Genome-wide association studies (GWAS) have identified more than 80 genomic regions influencing risk for chronic obstructive pulmonary disease (COPD). However, the functional genetic variants and the genes they influence within these COPD GWAS loci remain largely unidentified, thus limiting translation of these GWAS discoveries to new disease insights. Single genetic variants are unlikely to explain complex diseases, because perturbations of biological networks, not isolated genes, confer disease risk. These biological networks can be identified using bottom-up approaches that begin with the identification of functional genetic variants and the genes they influence, followed by animal model investigations of implicated genes. Using massively parallel reporter assays and chromatin conformation capture assays, we identified a functional variant in *FAM13A* within a COPD GWAS locus. We found that FAM13A binds to Beta-Catenin, and studies of the *Fam13a* knockout mouse confirmed connections to the Wnt/Beta-Catenin pathway. Biological networks can also be identified using top-down approaches, such as the determination of disease network modules within the protein-protein interaction network. We identified a 163 protein-protein interaction network module for COPD with COPD GWAS seed genes and random walk analysis, and then focused on a putative network connection between FAM13A and another COPD GWAS gene, TGFB2 (FAM13A-AP3D1-CTGF-TGFB2). We determined that FAM13A formed a complex with AP3D1 and TGFB2, and that FAM13A regulated secretion of TGFB2 in exosomes from bronchial epithelial cells. Thus, both bottom-up and top-down approaches to network building have identified new roles for FAM13A in COPD pathogenesis.

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Big Cancer Data in Cancer Systems Medicine

Cancer is increasingly considered a "systems" disease influenced by genetic, environmental and, to some extent, our microbiome. A grand challenge impeding successful treatment outcomes for cancer patients arises from the complex nature of the disease. We are, however, positioned uniquely to deal with this challenge given the mounting influx of quantitative data and clinical support tools. With clinical sequencing of tumors emerging as a mainstay in cancer care and treatment, we have the opportunity to apply the new and emerging field of Network Medicine, which applies systems biology and network science approaches to the dissection of molecular pathogenesis making precision medicine a reality. We used data from *cbioportal* and ICGC to apply the principles of Network and Systems Medicine to specifically address and answer the following questions: (a) starting from a set of known cancer driver genes (seeds) that harbor cancer hotspot mutations, can we expand the protein-drug space using the protein-protein interactome; (b) do closest-neighbor proteins to the seeds increase the protein-drug target space; (c) what is the role of mutations across race, sex and cancer type; and (d) can we design drugs as activators instead of inhibitors. Our results show the closest-neighbor proteins play a central role in expanding the protein-drug space. We also see a strong correlation between race, sex and cancer type with specific mutations at a higher prevalence in females than males. Using a regression model, we predict the probability of patient survival.

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