Network Medicine & Immunology

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Network Medicine

- «*Network medicine is the application of* **network science** *towards identifying, preventing, and treating diseases*»

- Biological networks
  - Protein-protein interaction networks (***interactome***)
  - Metabolic pathways
  - Disease networks (***diseasome***)
  - Epidemiological networks

The network paradigm

Complex systems are all around: society, economy, technological infrastructures and dynamics, living organisms

It is difficult to derive their **collective behavior** from the knowledge of the **system's components**

Their understanding can only be approached via **system thinking:** their mathematical description, prediction, and ultimately control is one of the **major intellectual and scientific challenges**

Behind each complex system there is an **intricate network** that **encodes** the **interactions** between the system's components

The network paradigm

- Networks **permeate** science, technology, business and nature

- We will never understand complex systems unless we develop a deep **understanding of the networks behind them**

- Surprisingly, most networks are driven by **common organizing principles**

Network Medicine

- WHAT: **Systems approach** (network & systems medicine, systems biology)

- WHY: **Aims**: better diagnoses, targeted therapies, better prognosis and prevention

- WHY: **P4 medicine** (Predictive, Preventive, Personalised and Participatory) → **One Health**

- HOW: **Interdisciplinarity**

- HOW: **Methods & data integration** (physics, statistics, informatics; molecular, genetic, multi-omic data, conventional patient data, clinical-pathological parameters)

- HOW: **Network paradigm**

Network Medicine

DATA! NETWORK!

GRAPH THEORY
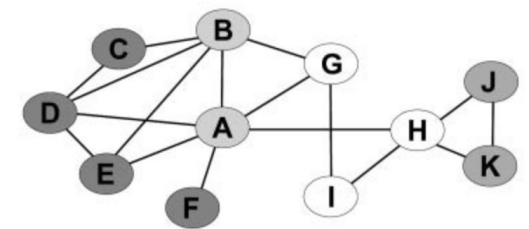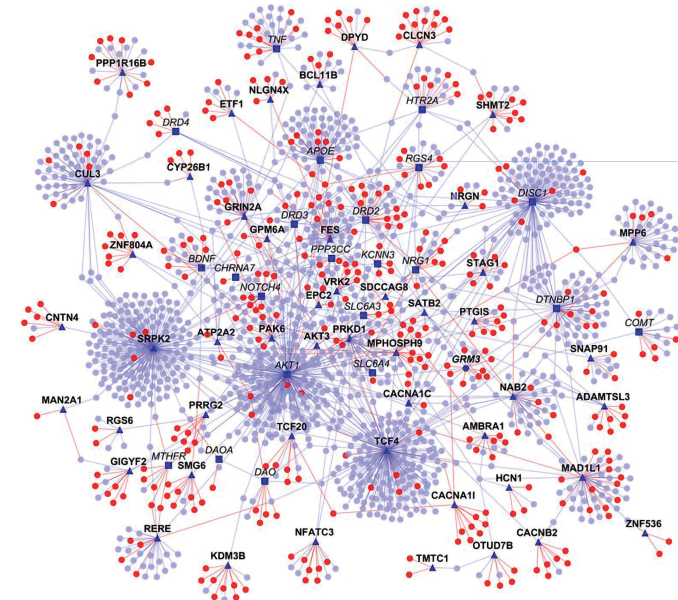
COMPUTATIONAL RESOURCES

MACHINE LEARNING, AI

IMMUNOLOGISTS, CLINICIANS, BIOLOGISTS, PHARMA!

Network biology & medicine

- Binary protein-protein interaction

- Reconstruction of the interactome

- Mathematical analysis (centralities, hubs, bottlenecks)

- Advanced statistical techniques (machine learning → predictions)

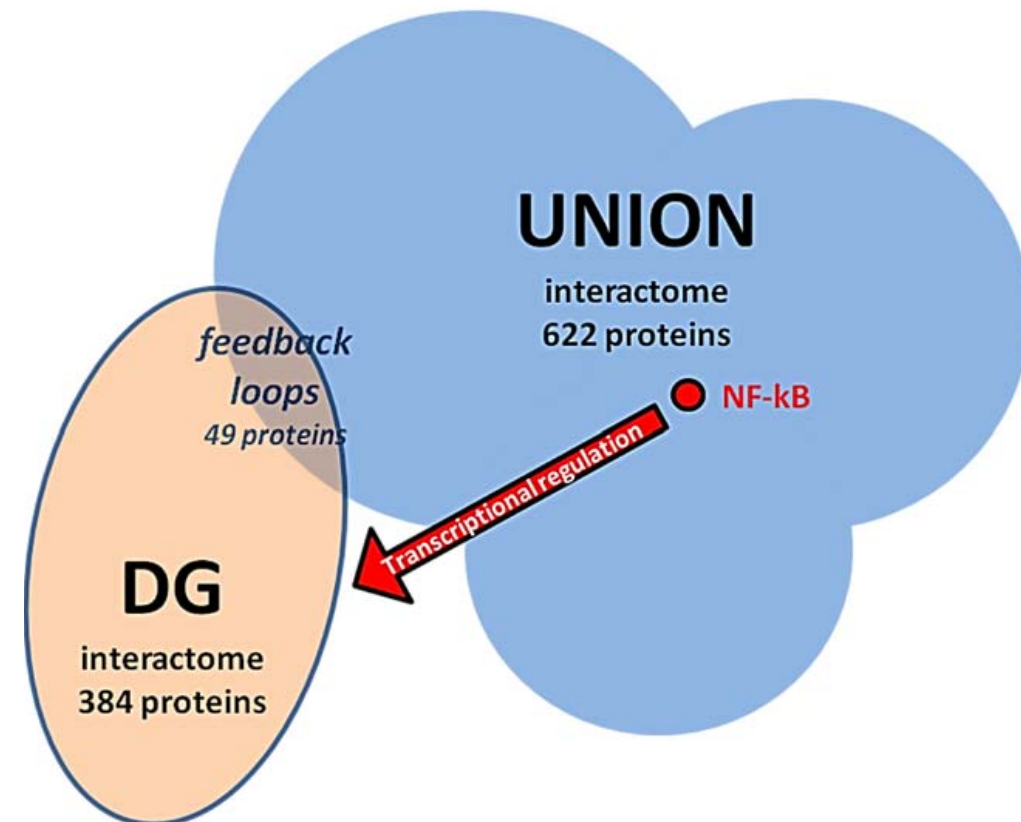# Charting the NF-κB Pathway Interactome Map

Paolo Tieri[1,2,3]*, Alberto Termanini[1], Elena Bellavista[1,2], Stefano Salvioli[1,2], Miriam Capri[1,2], Claudio Franceschi[1,2]

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- A wider, systemic picture of the NF-kB signaling system, master regulator of inflammation

- The complexity of the inflammatory process has escaped reductionist approaches
  - non-proportional kinetics
 - numerous and nested feedback loops

Charting the NF-kB interactome map

- NF-kB interactome: 622 proteins and 6115 interactions

- 441 downstream genes

- 13% of the identified NF- kB-regulated genes express proteins that play a direct role in the interactome

- Several neglected but topologically central proteins may play a role in the activation of NF-kB mediated responses
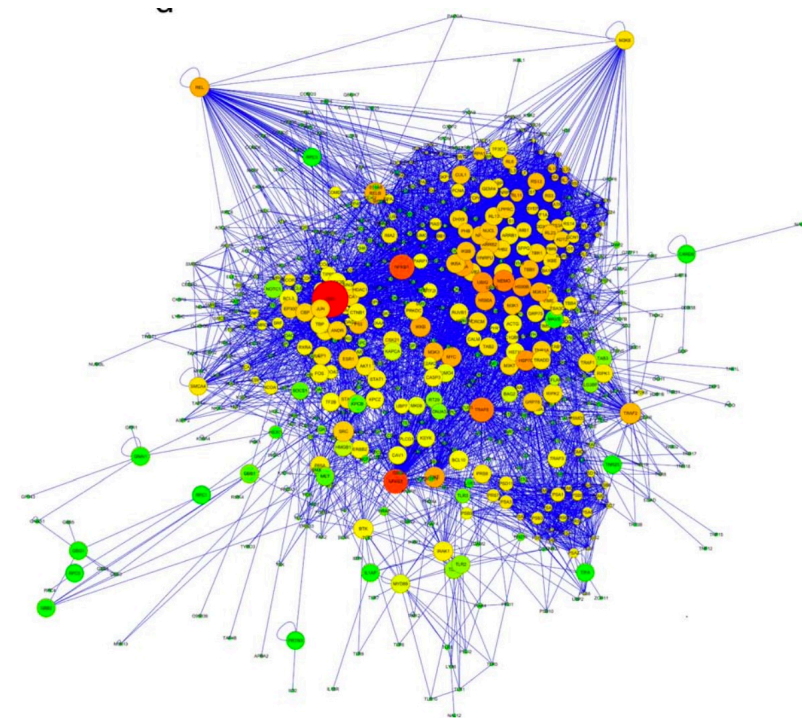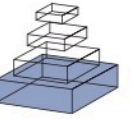
Multi-omic landscape of rheumatoid arthritis: re-evaluation of drug adverse effects

Paolo Tieri[1,2]*[†], XiaoYuan Zhou[2†], Lisha Zhu[2] and Christine Nardini[2]*

[1] IAC - Istituto per le Applicazioni del Calcolo "Mauro Picone," CNR - Consiglio Nazionale delle Ricerche, Rome, Italy
[2] Group of Clinical Genomic Networks, Key Laboratory of Computational Biology, Chinese Academy of Sciences - Max Planck Society Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Shanghai, China

- 6 main data sources

- 8 additional sources

- Integrated at the functional level of PPIs for the molecular framing of RA

- A single analytical picture of the known, yet complex, information about RA to provide a reliable platform for in silico hypothesis testing or recommendation on novel therapies

Multi-omic landscape of RA

- ~4000 selected molecules from 15 public databases, integrated and analyzed at the level of PPI
- Platform to
  - support in the identification of novel drug targets
  - support in the identification of potential contraindication to novel therapies
  - support in the design of robust clinical trials
- Virtual MTX treatment confirmed the 'impairment' of GI microbiome interface

frontiers
in Cell and Developmental Biology

Designing a Network Proximity-Based Drug Repurposing Strategy for COVID-19

Paola Stolfi[1], Luigi Manni[2], Marzia Soligo[2], Davide Vergni[1] and Paolo Tieri[1]*

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[2] National Research Council (CNR), Institute of Translational Pharmacology (IFT), Rome, Italy

- Prior knowledge:
  - Experimentally validated viral-host proteins
  - tissue-specific gene expression data
- Network analysis techniques: network propagation, connectivity significance

Data driven strategy for Covid-19 DR

- Network diffusion
  - exploits the concept of heat diffusion, i.e., how the heat distribution spreads over time in a medium, here consisting of the PPI network
- Connectivity significance
- Rank aggregation
- Tissue-specific gene expression filtering
- Integrated functional analysis & pharmacological setting
- **Disease gene prioritization → drug repuroposing proposal**

Drug	DrugBank ID	Target	Localization	Process	Type	Status	Indication	Other targets	Reference
Fostamatinib	DB12010	TBK1	Nucleoplasm, vesicles	Virus release	Small Molecule	Approved, investigational	Rheumatoid Arthritis and Immune Thrombocytopenic Purpura (ITP)	CTSL, ABL1, RPS6KA6, MET, TEK, TGFBR1, TGFBR2, SYK,	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fostamatinib-tablets-itp
		LYN	Golgi apparatus, Plasma membrane	Virus entry, virus assembly	Small Molecule	Approved	Pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease, and non-small cell lung cancer	KDR, LCK, SRC, PDGFRA, PDGFRB, FGFR1, FGFR2, FGFR3, FLT1, FLT3, FLT4,	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205832s010lbl.pdf
Nintedanib	DB09079	SRC	Plasma membrane	Virus entry	Small Molecule	Approved	Pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease, and non-small cell lung cancer (NSCLC)	FLT1, KDR, FLT4, PDGFRA, PDGFRB, FGFR1, FGFR2, FGFR3, FLT3, LCK, LYN,	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205832s010lbl.pdf
		FGFR1	Plasma membrane	Virus entry	Small Molecule	Approved	Pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease, and	FLT1, KDR, FLT4, PDGFRA, PDGFRB, FGFR1, FGFR2, FGFR3, FLT3, LCK, LYN,	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205832s010lbl.pdf
Pertuzumab	DB06366	ERBB2	Plasma membrane	Virus entry	Monoclonal antibody, Inhibitor	Approved	Metastatic HER2-positive breast cancer.		https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf

Thank you!