Human-Centered Drug Discovery: A Methodology To Identify And Validate High-Value Therapeutic Targets For Human Diseases

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BACKGROUND

Modeling diseases as networks has helped simplify an otherwise complex web of multi-cellular processes; however, an exclusive reliance on symmetric relationships in these networks overlooks the existence of disease continuum states and loses information relevant to pathogenesis and for the development of therapeutics. Network-based analyses severely influenced by symmetric analyses have helped formalize Network Medicine as a field and deliver many successes, but drugs that can predictably re-set the network in complex multi-component diseases are yet to emerge.

TECHNOLOGY DESCRIPTION

To overcome the deficiencies of the modeling system described above, Researchers at UC San Diego have developed an asymmetric invariant Boolean implication relationships to create a different kind of network and demonstrate its ability to detect, define and explore the fundamental time series underlying any biological data, and to unravel disease continuum states that otherwise go unrecognized. The researchers use such data for predicting outcome, target identification, guiding the choice of pre-clinical models for target validation and for designing organoid-based disease models.

APPLICATIONS

The invention provides a method for therapeutic target validation in network rationalized animal models that most accurately recapitulate the human disease.

ADVANTAGES

The inventors have provided an innovative blueprint of a human-centered network-based drug discovery approach that differs from the current practice in three fundamental ways, as listed below using the broken gut barrier in inflammatory bowel disease (IBD) as an example.

- Target identification and prediction modeling that is guided by a Boolean implication network of continuum states in human disease.
- Target validation in network-rationalized animal models that most accurately recapitulate the human disease.
- Target validation in human pre-clinical organoid co-culture models, inspiring the concept of Phase '0' trials that have the potential to personalize the choice of therapies.

STATE OF DEVELOPMENT

To showcase the powerful and superior nature of this approach over other conventional methods, the researchers exploited it as a drug-discovery platform to solve an unmet and urgent grand challenge, i.e., inflammatory bowel disease (IBD). Despite being at the forefront of biomedical research, little to nothing was available to fundamentally tackle the most widely recognized indicator/predictor of disease relapse, response and remission, i.e., a compromised epithelial barrier. They identified stress-induced disruption of the polarized state of the epithelial barrier as an invariant early continuum event in IBD and identified a target that was predicted to restore/protect gut barrier function. Predictions were validated in network-rationalized preclinical mouse colitis and human organoid models. Evidence presented also rationalizes the use of Boolean implication networks for precision drug discovery and demonstrates the superiority of such approach over traditional approaches.

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations

PATENT STATUS

Patent Pending

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OTHER INFORMATION

KEYWORDS

IBD, Boolean implication networks, drug development, organoid-based disease models, human disease models, therapeutic target validation

CATEGORIZED AS

- **Medical**
  - Disease: Autoimmune and Inflammation
  - Disease: Digestive System
  - Screening
- **Research Tools**
  - Animal Models

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