Tissue Dynamics

Disruptive Drug Development

Sensor Illuminated Drug Development

Metabolic imbalance as a novel mechanism of disease

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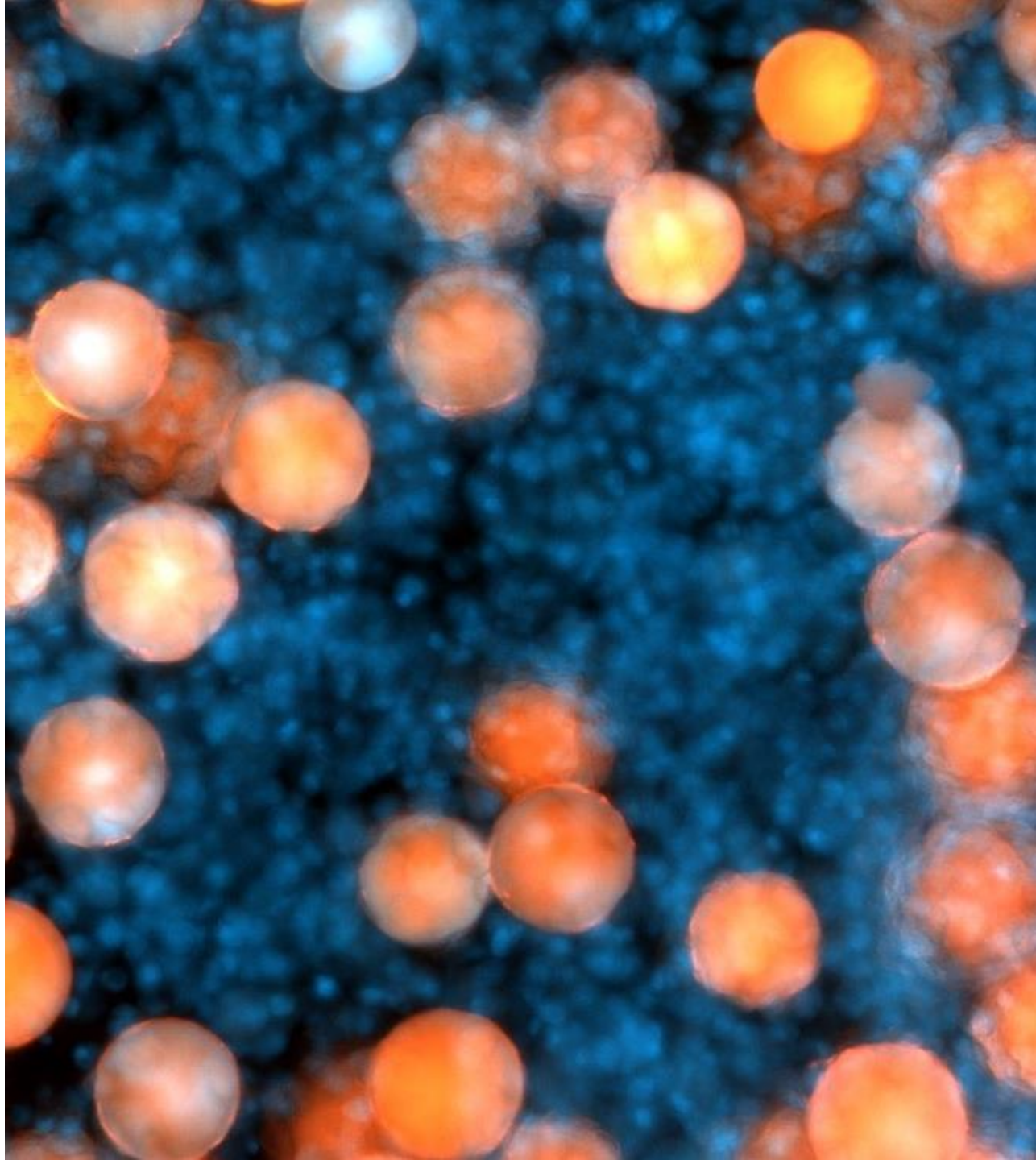


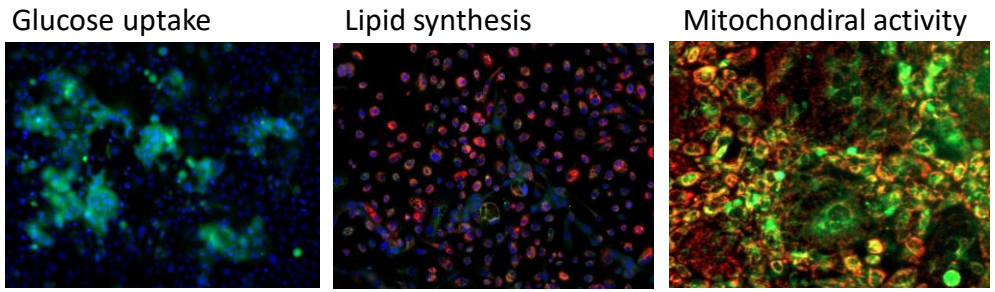
New Generation of Drug Development

Tissue Dynamics (TD) is a drug development company, with a proprietary platform allowing:

- Rapid determination of metabolic imbalances driving human disease
- Direct identification of unique protein targets for intervention
- Animal-free human-relevant drug-discovery, efficacy validation and safety assessment

Tissue Dynamics

Disruptive Drug Development



Our Team

Prof. Yaakov Nahmias

Director, Alexander Grass Center for Bioengineering HU, Jerusalem

Founder & CSO

Recipient of:

- NIH career award
- 2 ERC grants
- Rappaport Prize for Biomedical Sciences
- Rosetrees Trust Prize
- Kaye Innovation Award

Dr. Einat Zisman

CEO

Previous positions:

- FutuRx (Israel Biotech Incubator), CEO
- Hadasit (Hadassah TTO), CEO
- Yeda (Weizmann Institute's TTO), CBO
- 8400 Cohort #1 member

Avner Ehrlich

EVP R&D

- Bio-engineering experience
- MADA excellence PhD Program
- Dean's list of excellence for academic achievements

Dr. Yafit Stark

Regulatory & Clinical Development

Previous positions:

- Vice President, Teva Pharmaceutical Industries, Ltd.
- Chief Clinical Officer and Head of Oncology, Emerging Therapeutic Areas and Biogenerics Innovative R&D

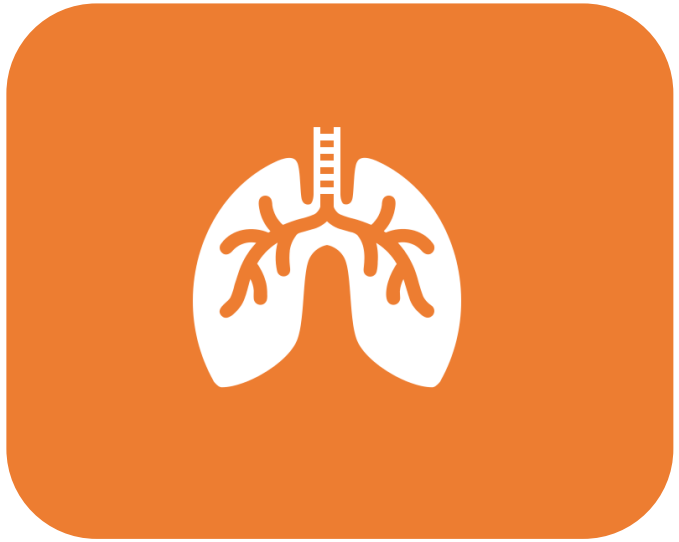
The Need

- Human tissues require constant production of energy and macromolecules to maintain their function
- Accumulating evidence suggests that disruption of human-specific metabolic processes is the driver of myriad of disease processes ranging from degenerative disorders, to cancer, cardiovascular events and viral infections
- Efforts to target metabolic pathways are often frustrated by the complexity of metabolic networks, and inadequate cellular and animal models

There is a need to identify metabolic imbalances in human relevant disease models and provide validated novel targets for intervention

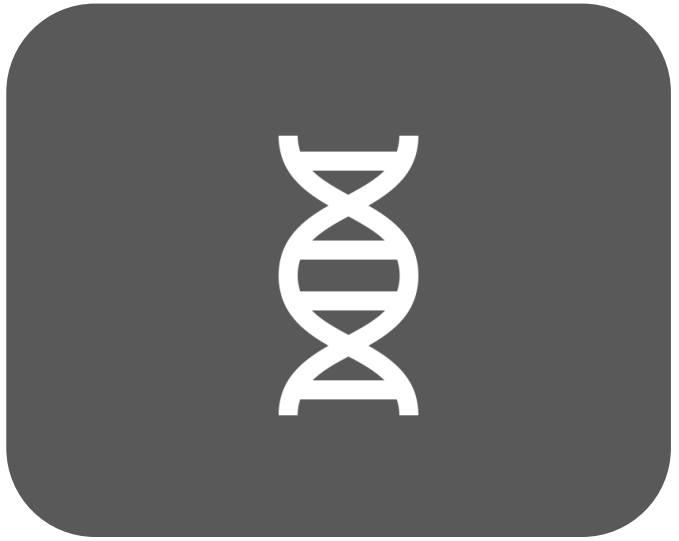
The Solution

Critical integration of sensors, human on chip and advanced genomics



Validated 3D human models of liver, kidney, lung, heart & brain[1]

Sensor-based monitoring of metabolic pathways[1]



Genome-wide CRISPR screen for metabolic-targets (GeMTL)[2]

1. *Bavli et al. PNAS. (2016) | Cohen et al. Science T.M. (2021)*
2. *Levy et al. Nature Biotechnology (2015) | Shalem et al. Science (2014)*

TD Platform Road Map

Drug development for NAFLD based on novel targets identified in the GeCKO screen of metabolically functional human liver cells, applying microtissue and sensing for target validation and drug safety assessments

Next steps 2021-2023

Extend GeMTL to additional pathological phenotypes, confirmed across diverse genetic backgrounds and mapped against libraries of drugs and tool compounds for precision medicine

Fully automated closed robotic system, advanced integrated software

Additional organs: Cardiac, brain
More genetic origins

Microtissues

Primary hepatocytes, proximal kidney, lungs

Metabolic sensing

System includes embedded microchips, sensors, temp., flow, oxygen control for 30 days

GeMTL - NAFLD

- Identified new molecular targets that disrupt fatty liver disease in two genetic backgrounds
- A tool compound for one of the targets prevented lipid accumulation

Clinical Validation

- Fenofibrate for COVID19-triggered severe inflammation
- SGLT2 inhibitors for nephrotoxicity induced by platinum-based chemotherapy
- Novel MOA for acetaminophen hepatotoxicity

Platforms capabilities **current** status

Platform Validation: Treating severe COVID-19 patients: Target Identification and Drug Repurposing

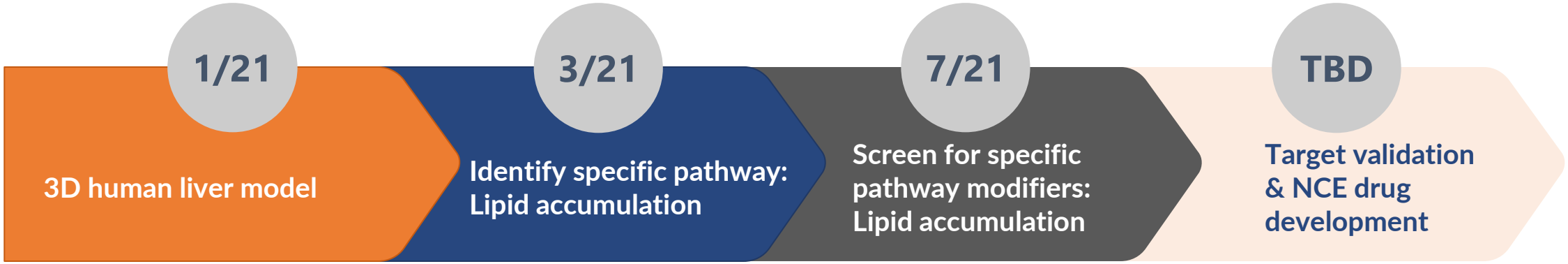
Metabolic imbalance identified to cause onset of inflammation: Increased lipid accumulation due to decreased catabolism

Fibrates that activate lipid catabolism through PPARα found to reverse lipid accumulation, and reduce viral load in the human lung model

COVID-19 patients taking fibrates found to show significant faster recovery and lower immunoinflammatory response

Severe hospitalized COVID-19 patients treated with nanocrystallized fenofibrate showed dramatic reduction in inflammatory stress and 3-fold faster recovery

Pipeline: Identification of novel targets for fatty liver disease (NAFLD)



Characterizing the metabolic imbalance caused by unbalanced, high glucose and fat diet in a metabolically-relevant human model

Excess lipid intake results in metabolic imbalance and lipid accumulation, intervention should reduce lipid accumulation in the presence of unbalanced diet

Genome-wide CRISPR screen identified several targets for intervention to reduce lipid accumulation in an unbalanced diet model

Planned

Unpublished data

Company Overview

- **Human-specific** metabolic pathways as drivers of pathophysiology
- Unique platform permitting rapid elucidation of molecular **mechanism of action**
- **Novel target discovery** based on Genome-scale CRISPR Knock-Out (**GeCKO**) of primary hepatocytes enabling an AI tool of **metabolic-targets libraries**
- Advanced **organ on chip** models of fatty liver disease, cardiac arrythmia, ischemic injury, virus infection, renal dysfunction, glioblastoma and more
- Fully integrated clinically-relevant animal-free **safety assessment process**
- Demonstrated POC & potential for rapid 505(b)(2) drug repurposing & lifecycle management
  Established **pharmaceutical pipeline** and strategic partnerships

Thank You

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