Boehringer Ingelheim

Why we need a patient-centric approach to **CardioMetabolic Disease Research and Development**

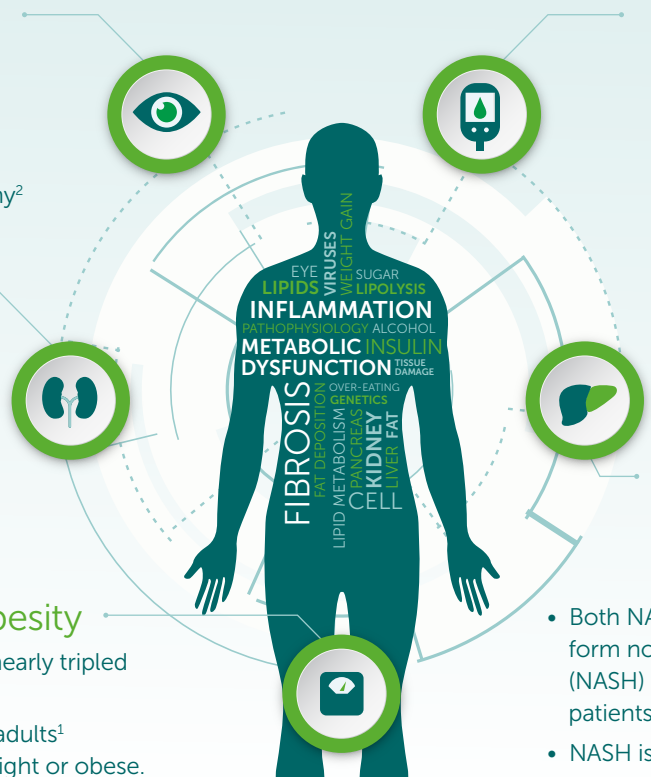
Patients with cardiometabolic diseases often have multiple conditions connected by underlying similar pathologies

Diabetic Eye Diseases

- Diabetic retinopathy is the leading cause of vision loss in adults[2]
- One-third of patients with type 2 diabetes have diabetic retinopathy[2]

Diabetic Kidney Disease

- Diabetes, hypertension and kidney disease are highly interlinked
- Up to 40% patients with type 2 diabetes will develop chronic kidney disease[2]



Type 2 Diabetes

- Affects 425 million people worldwide[2]
- 1 in 10 adults estimated to have diabetes by 2040[2]
- Complications include increased incidence of stroke and heart attack, kidney disease, diabetic retinopathy, liver disease[2,3]
- More than half of patients with type 2 diabetes are obese[4]

NASH

- Global prevalence of non-alcoholic fatty liver disease (NAFLD) is currently estimated to be 24%[5]
- Both NAFLD and the more serious form non-alcoholic steatohepatitis (NASH) are highly prevalent among patients with type 2 diabetes
- NASH is expected to become the most common cause of advanced liver disorders, eventually necessitating liver transplantation, in the coming decades

Overweight & Obesity

- Worldwide obesity has nearly tripled since 1975[1]
- In 2016, nearly 2 billion adults[1] worldwide were overweight or obese.
- About 13% of the world's adult population were obese in 2016[1]

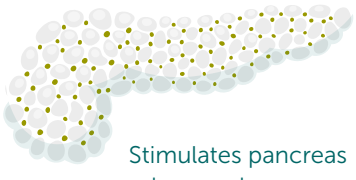
3 key processes are involved in the progressive development of **CardioMetabolic Diseases**

By exploring disease mechanisms and common pathways within various cardiometabolic diseases, we aim to create synergies across our research programs.

Our holistic approach gives us the opportunity to explore a number of different research fields, allowing us to prioritize the most promising avenues of discovery, as we pursue the next wave of innovative medicines.

1 METABOLIC DYSFUNCTION

2 main factors contribute to metabolic dysfunction: **genetics and over-eating**



Stimulates pancreas to secrete more insulin to cope with raised glucose levels

Raised blood sugar

Weight gain (visible)

Changes in lipid metabolism stimulate peripheral lipolysis

Leads to subcutaneous and visceral fat deposition

THIS CAN CAUSE AN **INFLAMMATORY RESPONSE**

Our Research in Metabolic Dysfunction

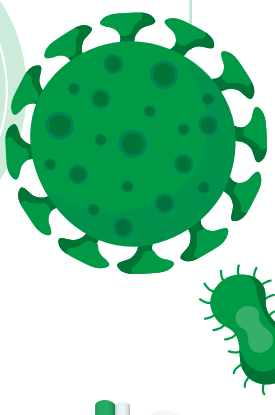
We are applying cutting edge science to address significant unmet medical need in obesity and type 2 diabetes.

Several research collaborations contribute to our work in this area. For example, together with ETH Zurich we are exploring the molecular foundations of these conditions and in collaboration with Zealand Pharma and Gubra we are investigating novel peptidic compounds for the treatment of obesity and type 2 diabetes.

2 INFLAMMATION

Raised lipids and **increased fat deposition** can cause inflammation

Inflammation can also be caused by other factors such as **alcohol** or **viruses**

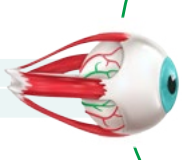


Our Research in Inflammation

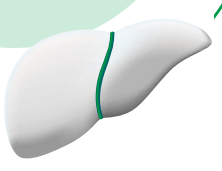
Our research approach directed towards the inflammatory pathways may have potential in multiple indications.

3 FIBROSIS

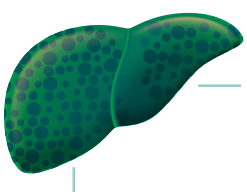
CHRONIC INFLAMMATION LEADS TO CELL/TISSUE DAMAGE AND ACTIVATES THE **FIBROTIC PROCESS** (TISSUE SCARRING)



Inflammation in the **liver, kidney** and **eye** is a key component in the pathophysiology of several diabetic complications



Progressive development of fibrotic tissue leads to



liver cirrhosis

chronic kidney disease and kidney failure

Our Research in Fibrosis

We are committed to accelerating research in fibrosis and are exploring novel pathways and new therapeutic approaches to address the significant unmet medical need in this area.

Working together with Dicerna Pharmaceuticals, we are investigating new approaches that address previously inaccessible drug targets to protect and restore liver functionality in NASH and fibrotic liver disease. Our partnerships with the Harvard Stem Cell Institute/ Harvard Fibrosis Network and Hydra BioSciences explore novel pathways and molecular targets for the treatment of NASH and chronic kidney disease.

Putting patients at the heart of innovation in **CardioMetabolic Disease Research and Development**

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5. Younossi, Z. M. *et al*. Global epidemiology of nonalcoholic fatty liver disease — meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 64, 73–84 (2016).

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