



# LIFE Child – Spin off KFO proposal

## Growing up - Signals and Mechanisms of Abnormal Growth in Children

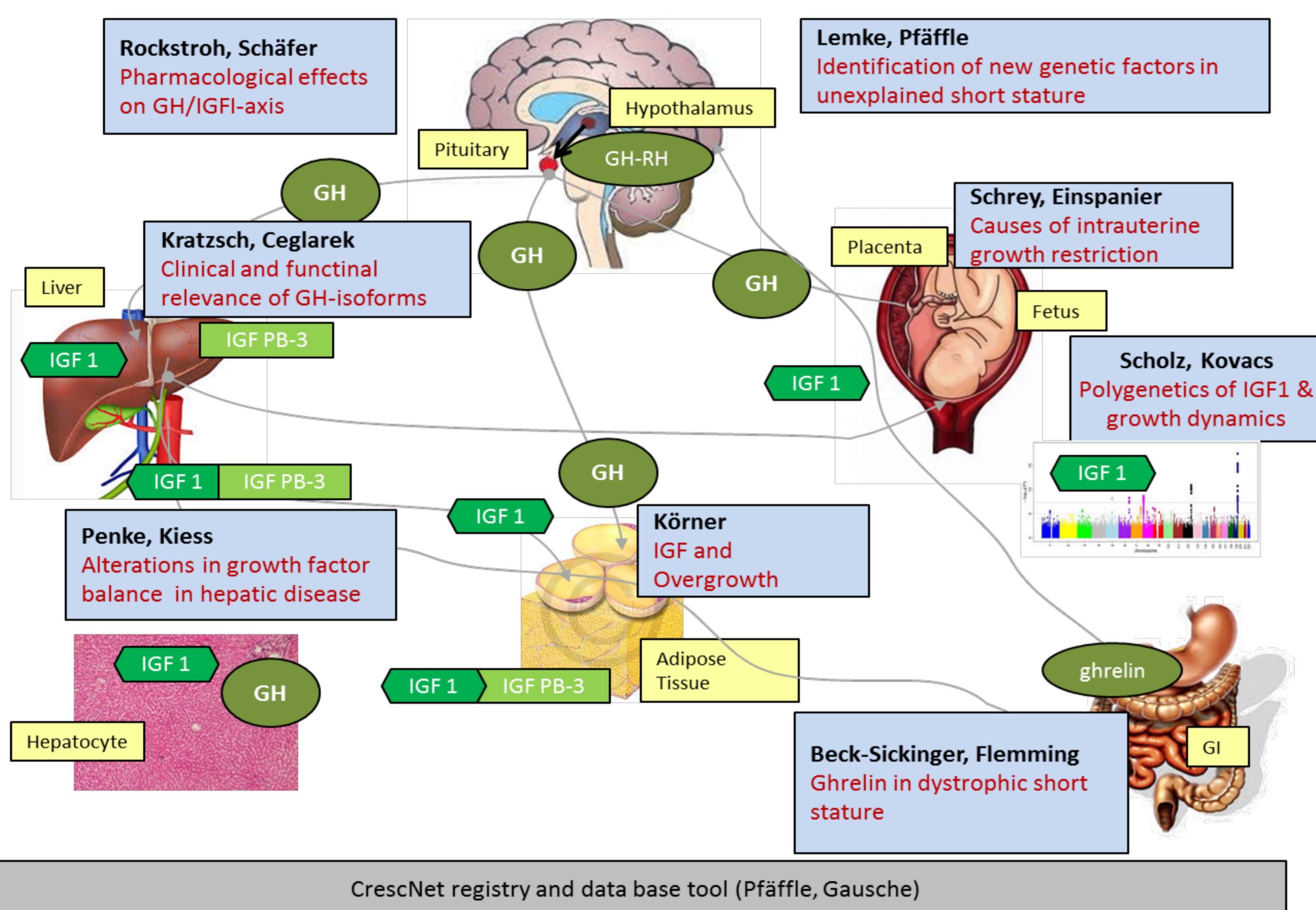
Leiter: Antje Körner

### AIM

We focus on the clinical question: **What are the mechanisms of abnormal growth and unexplained short stature in children ?**

For this, we collaboratively study the signals and underlying mechanisms which communicate, predict and/or directly affect growth as a consequence of malfunctioning of signalling pathways and underlying disease. This approach will take into account (epi)genetic modulators, endocrine signals, and underlying disease and will study how these different factors finally converge to the major growth promoting (GH-Insulin/IGF)-pathway.

### PROJECTS



#### Lemke MD (Humangenetik)/Pfäffle MD (Kinderklinik):

will investigate genetically determined developmental malformations of the brain and the pituitary (co-)affecting the GH axis and aim to identify and characterize new genetic candidates. Well characterized cohorts are available along with the combined expertise of clinical genetics and molecular biology workup.

#### Kratzsch PhD (ILM)/Ceglarek PhD (ILM):

this project will investigate the existence and biological/analytical/clinical relevance of isoforms of growth hormone. The endocrine analytical expertise is accompanied by profound pediatric endocrinologic expertise in patients.

#### Rockstroh PhD (Kinderklinik)/Schäfer MD (Pharmakologie):

considering that many drugs, particularly psychopharmaka, are suspected to affect growth beyond the underlying disease for which they are used, it is of interest to investigate the direct effect of pharmacological compounds on the GH-IGF axis (signaling). This project combines pharmacologic expertise (including compound repository) with molecular expertise on IGF1 signalling.

#### Scholz PhD (LIFE)/Kovacs PhD (IFB):

The major determinant for height is polygenetic, although the explained variance of height from candidate and genomewide approaches is rather unsatisfactory. This may be due to the fact that the studies have been performed in adults not taking into account major covariates such as parental/target height. We hypothesize that investigating IGF1 as target trait in polygenetic analyses will help to refine candidates and to develop customized target ranges for IGF1 on a familial background. In addition to IGF1, we will perform epigenetic studies and assess growth dynamics in children.

#### Schrey MD (Frauenklinik)/Einspanier PhD (Vet.med.):

Besides genetic/familial predisposition, being born small for gestational age is a risk factor not only for sustained growth retardation. The project aims to identify risk factors and (molecular) markers for IUGR with special emphasis on prenatal stress following a translational approach by investigating at risk children (identified already during pregnancy), investigating molecular signatures in placenta-cord blood-peripheral blood and associating it with the clinical course of the children catch-up regarding growth. This is complemented by animal studies on the effect of prenatal stress on growth restriction in offspring.

#### Penke PhD (Kinderklinik)/ Kiess MD (Kinderklinik):

The aim of the study is to test whether or not NAD metabolic enzymes could be novel therapeutic targets to restore normal hepatic IGF production in obesity associated childhood obesity.

#### Körner MD (Kinderklinik):

Besides the classical components of the GH-IGF1 axis, the adipose tissue contributes to the endocrine and metabolic phenotype affecting altered growth. By investigating the association of GH-IGF1 contribution of the adipose tissue we aim to explain the altered/accelerated growth in obese children.

#### Beck-Sickinger PhD (Biochemie)/ Flemming MD (Kinderklinik):

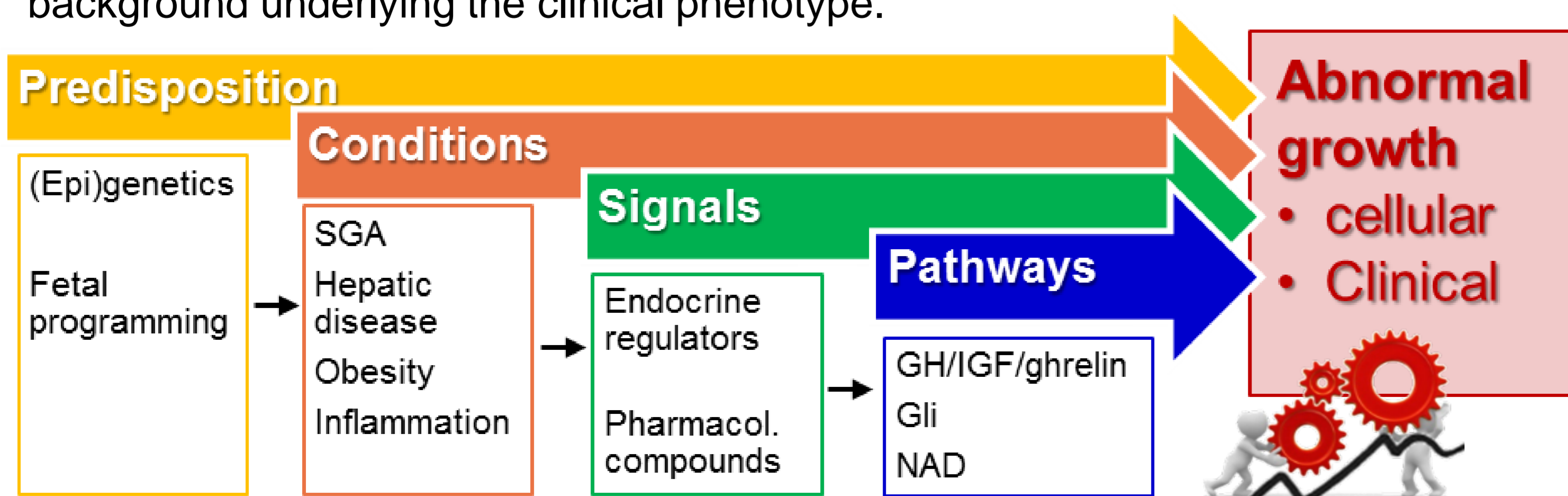
Investigation of the functional and clinical relevance of the gut derived hormone ghrelin that signals centrally through the GH-receptor. Dysregulation of ghrelin in chronic inflammatory bowel disease is hypothesized to profoundly affect GH-axis and/or nutritional deprivation with subsequent growth retardation in these chronically ill children.

#### Z CrescNet

IT backbone for integrative patient/cohort management and clinical phenotyping.

### RATIONALE & APPROACH

- Growth is a genuine and central issue for child health and pediatric medicine.
- Clinically, normal growth is a hallmark of normal development whereas deviation from normal growth points to potentially underlying disease.
- Biologically, growth is the consequence of cascades of proper functioning of determination, environment, substrate supply, differentiation, regulation, modulation and systemic organization.
- Besides an underlying genetic background, exogenous and endogenous signals converge to regulate or modulate growth on the molecular, cellular and systemic level.
- Such factors may often act at critical periods or over the entire time span of development starting prenatally through critical periods of early child development and puberty to young adulthood.
- The approach of the research group encompass clinical projects that longitudinally monitor growth, identify patients or clusters of patients with deviations and serve as human models. The translation to mechanistic workup is direct, including patient material, animal models and cell/molecular biology to investigate the mechanistic background underlying the clinical phenotype.



#### Institutions involved:

- Klinik und Poliklinik für Kinder und Jugendliche
- Institut für Humangenetik
- Institut für Laboratoriumsmedizin, Klinische Chemie und Molekulare Diagnostik
- Institut für Pharmakologie
- Universitätsfrauenklinik
- LIFE
- IFB AdipositasErkrankungen
- Institut für Biochemie (BiPhaPs)
- Institut für Veterinärmedizin