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**089-30622-301**

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# ERC starting grant

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Max-Planck-Institut für Psychiatrie

- **2007 – RG leader MPI Psychiatry**
  - **2008 -1. application/panel LS5 - neuroscience**
    - *'Genetic determinants of stress hormone response and unipolar depression'*
    - **Upload error**
      - **The binding statement from the Host Institution was missing.**
  - **2009 – 2. application**
    - **same title, only small changes to 2008**
    - **>2 points each for research project and PI each**
    - **No interview**
    - **Too „hypothesis generating“**
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# ERC starting grant

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Max-Planck-Institut für Psychiatrie

- **2010 – 3. application**
    - **Gene x environment interactions in affective disorders – elucidating molecular mechanisms**
  - **Except for 1 aim, all different**
  - **Focus on one central hypothesis and follow-up on several levels**
  - **Invited for interview and selected for funding**
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Max-Planck-Institut für Psychiatrie

# ERC Starting Grant

**Gene x environment interactions in affective disorders –  
elucidating molecular mechanisms**

**GxE molmech**



MAX-PLANCK-GESELLSCHAFT

**Elisabeth Binder**

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# Overview curriculum vitae

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Max-Planck-Institut für Psychiatrie

## Medical

- MD (MUW/ULB *Vienna/Brussels*)
- Psychiatry/Neuroendocrinology (MPI Psychiatry *Munich*)

## Neuroscience

- PhD (Emory University *Atlanta/USA*)

## Human Genetics

- Post-doctoral work (MPI Psychiatry/TUM *Munich*)

## Currently

- group leader (W2) at Max-Planck Institute of Psychiatry
- Assistant Professor Emory University School of Medicine
- **Triple education important for successful translational research**

- **Recent achievements**

Ressler...*Binder*, May. 2011 *Nature* – new gene/biomarker for post traumatic stress disorder (PTSD)

Kohli...*Binder*. 2011 *Neuron* – new candidate gene for unipolar depression

Metha...*Binder*. 2011 *Archives of General Psychiatry* – new biological subgroups of PTSD

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# Stress/trauma-related psychiatric disorders



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- High life time prevalence
  - unipolar depression 10-20%
  - post traumatic stress disorder (PTSD) 3-10%
- Pathophysiology?
  - Genes and Environment
- Treatments insufficient
- High burden on individual and society

**Understanding of risk and resilience factors for stress-related psychiatric disorders**

**New therapeutic approaches**

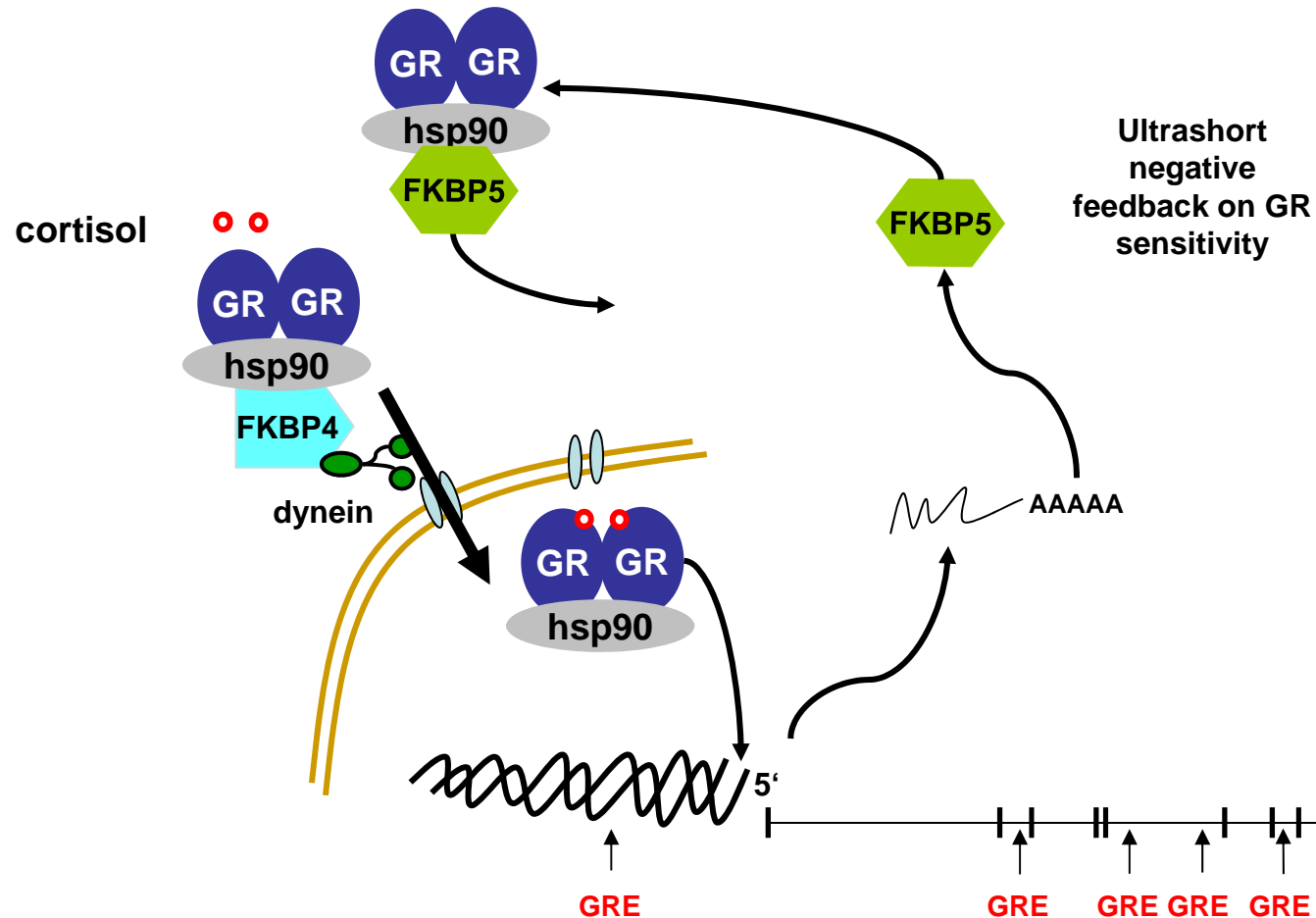


# FKBP5 and stress-related disorders



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## FKBP5 – a regulator of glucocorticoid receptor function



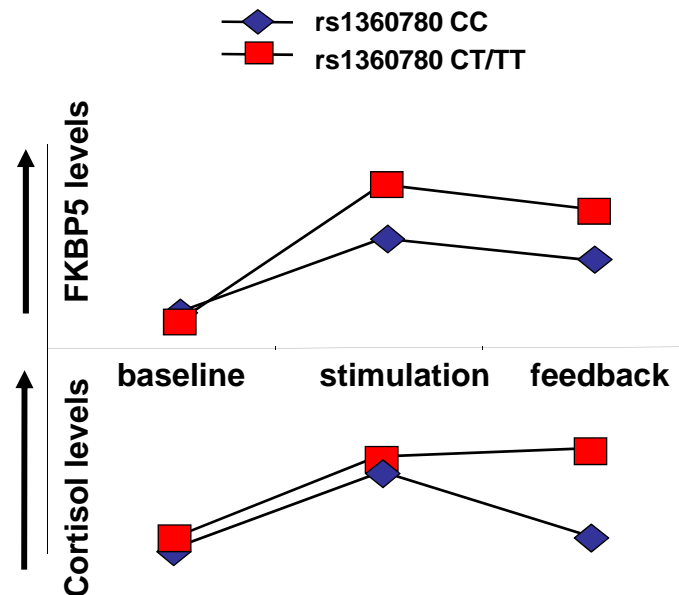
## Glucocorticoid response elements in *FKBP5*

# Polymorphisms in FKBP5 locus

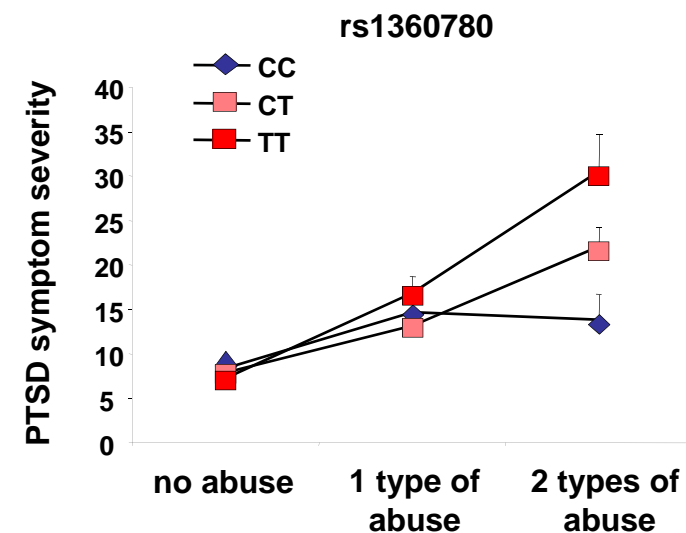


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- alter FKBP5/GR feedback loop (Binder et al., *Nature Genetics* 2004)
- Alter GR sensitivity and cortisol response after stress (Binder et al., *JAMA* 2008, Ising et al., 2008)
- interact with early trauma to predict psychiatric symptoms (Binder et al., *JAMA* 2008, Xie et al., 2010)
- define inherent risk and resilience to stress/trauma (Binder *Psychoneuroend.* 2009)



**Molecular and endocrine effects**



**Psychiatric effects**

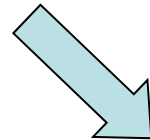


# Molecular mechanisms of stress x gene interactions?

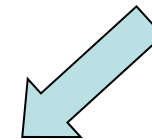


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Genetic  
polymorphisms

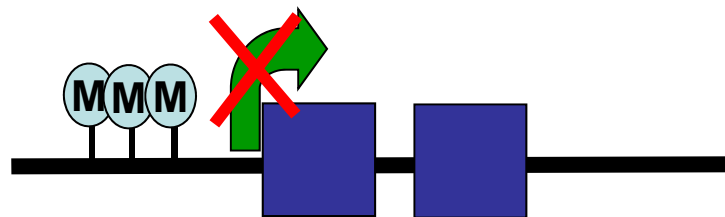


Environment



Stress related disorders

DNA methylation C<sup>met</sup>G



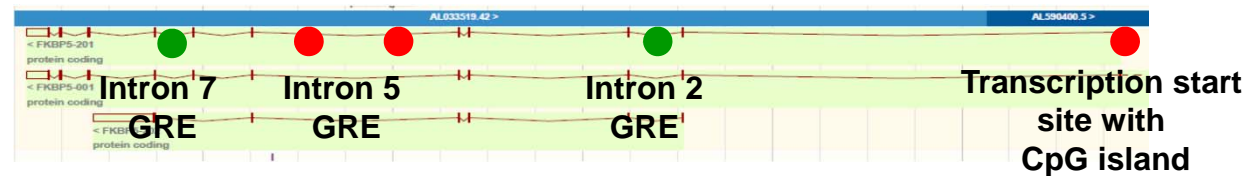
FKBP5 risk allele + early trauma = prolonged GR activation  
= DNA demethylation

# Allele-specific DNA demethylation in FKBP5 locus may mediate GxE

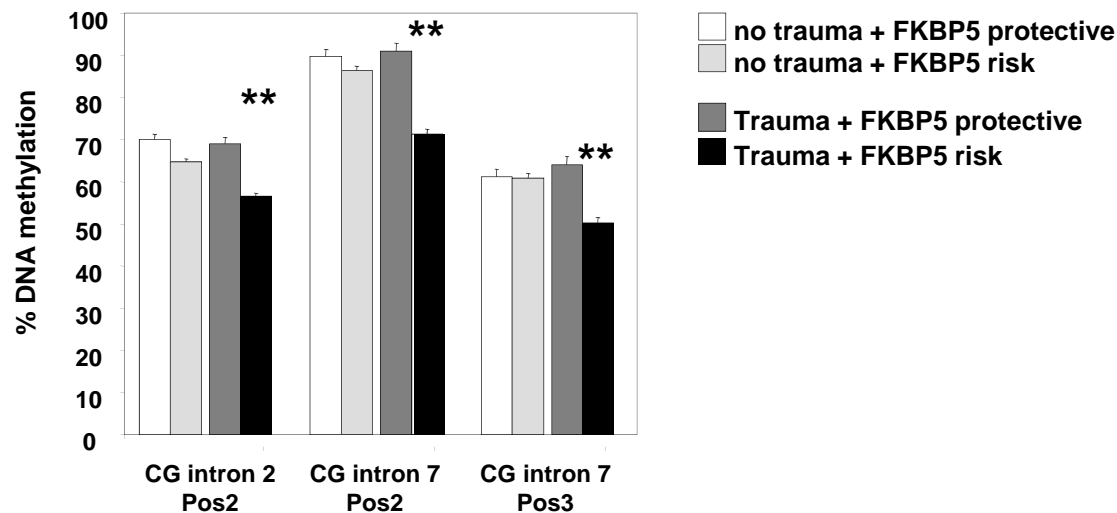


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1. 10 CGs in GREs of FKBP5 are methylated – 50-90%



2. CGs are de-methylated in risk allele carriers with trauma exposure



3. Functionality of GRE methylation supported by reporter gene assays

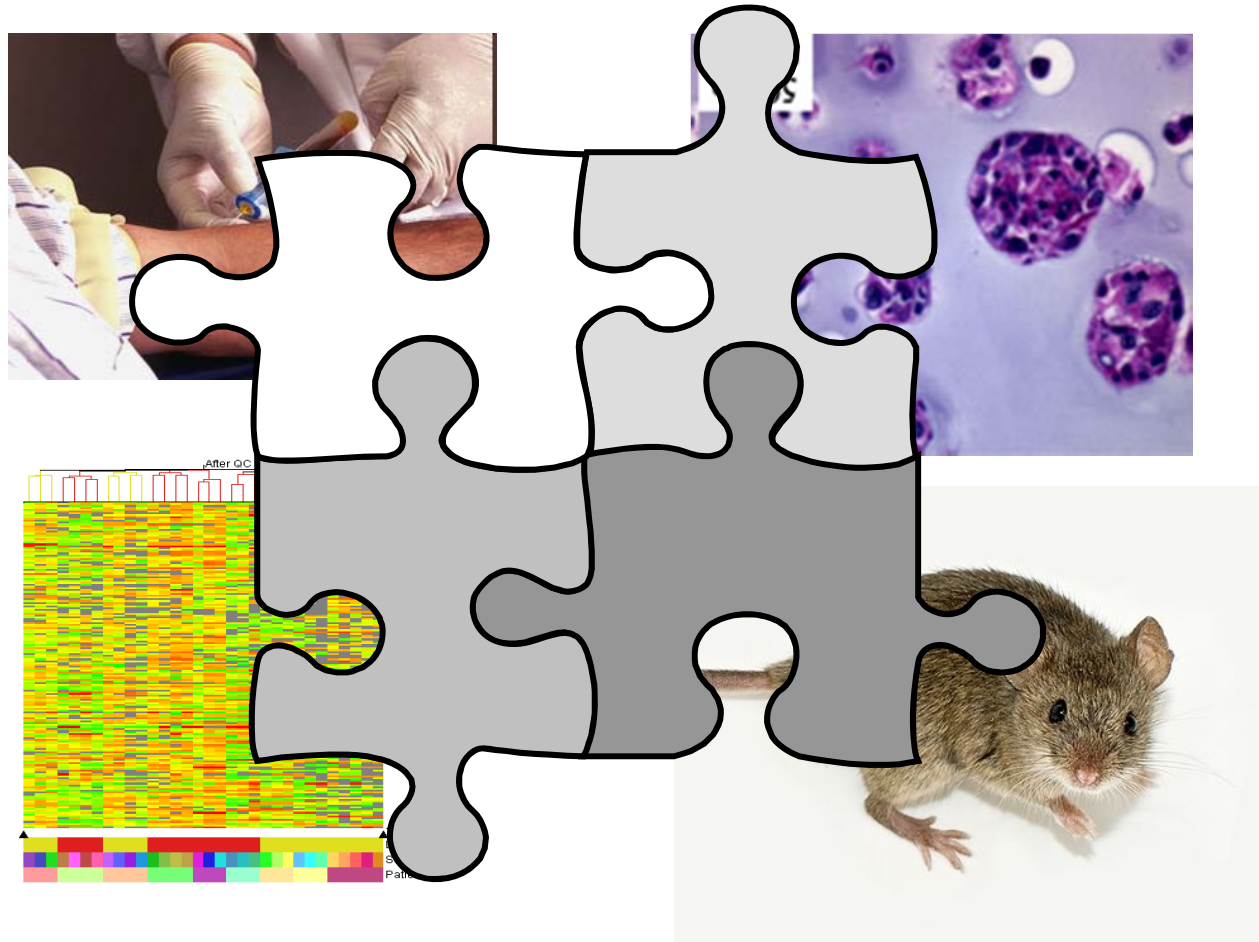
# Translational approach – GxE molmech



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**Clinical research**

**Cell lines**



**High throughput  
genomics**

**Animal models**

# Aims of ERC proposal



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## 1. Further characterization of FKBP5 GRE methylation in human tissue

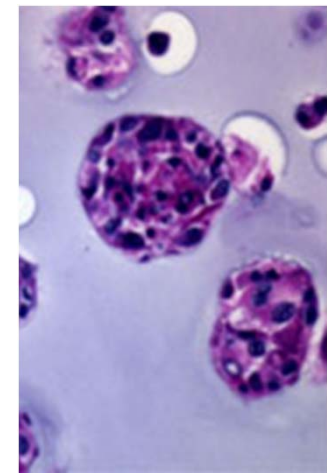
### a) *FKBP5 methylation and GR/FKBP5 feedback*

FKBP5 methylation in peripheral blood and molecular and systemic/endocrine measures *in vivo*



### b) *Allele-specific demethylation – GR activation or methyl CpG-binding domain (MBD) proteins?*

Effects of prolonged GR stimulation and genotype on FKBP5 methylation and MBDs (MeCP2) in cell lines



# Aims of ERC proposal



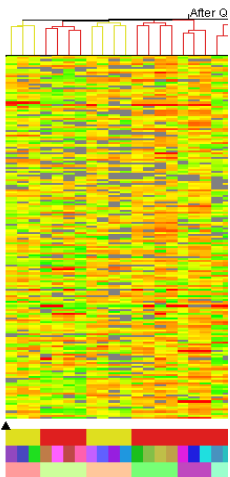
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## 2. Do rare variants in FKBP5 contribute to GxE interactions?

Next generation sequencing in 400 traumatized individuals

Genotype variants in large sample (N = 5000) for GxE interactions

➔ **Function of FKBP5 – transgenic animal models**



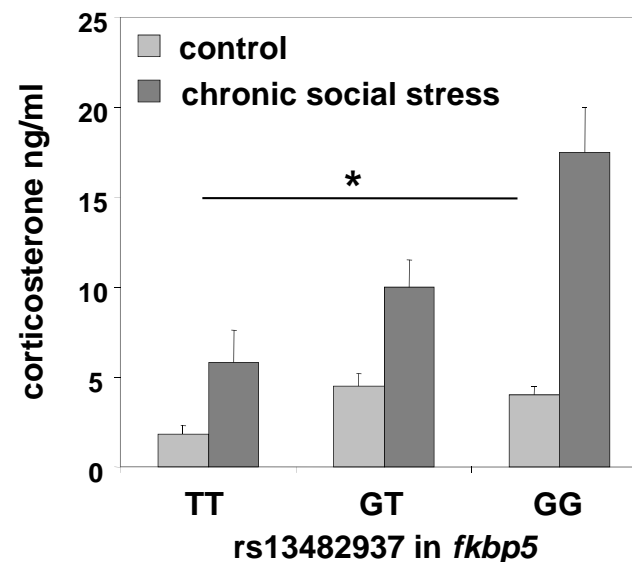
# Aims of ERC proposal



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## 3. Can FKBP5 x early trauma interaction be modeled on molecular level in mice?

Mouse *fkbp5* SNPs + chronic social stress = longterm stress hormone hyperactivity



molecular correlates of FKBP5 x stress interaction in **blood and brain**

**More face validity** than genetic or environmental manipulations alone

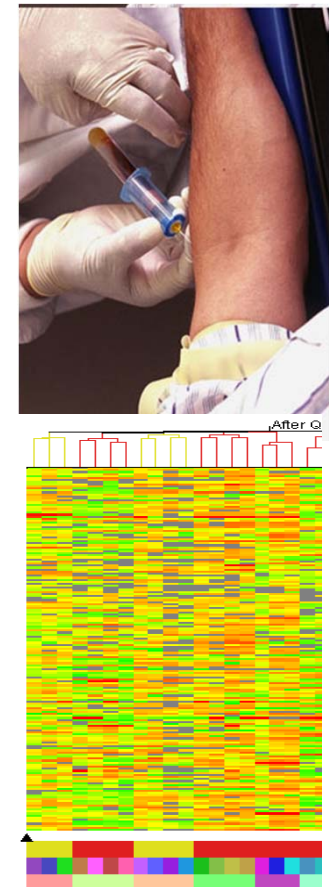
# Aims of ERC proposal



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## 4. Can analogue mechanisms be detected for other GR-responsive genes?

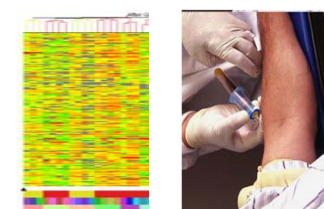
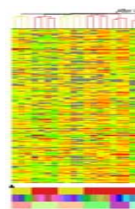
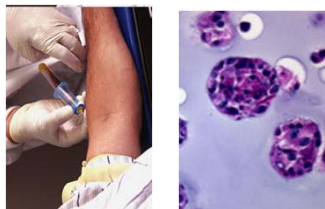
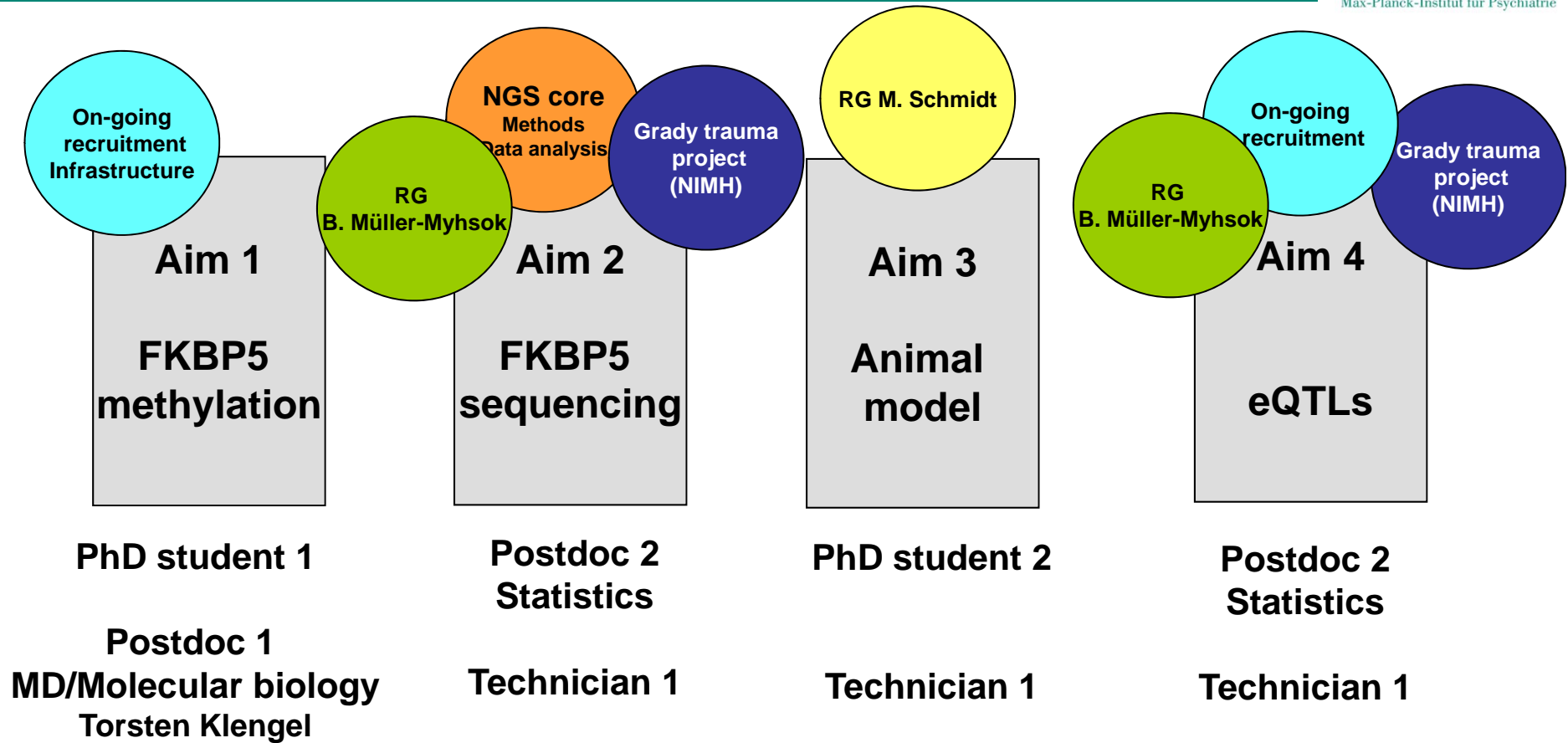
- Expression quantitative trait loci (eQTLs) for **GR-stimulated gene expression** in peripheral blood
- top eQTLs in GxE study of 5000 individuals for association with psychiatric disorders
- **Allele-specific methylation** of candidate genes



# Team and support



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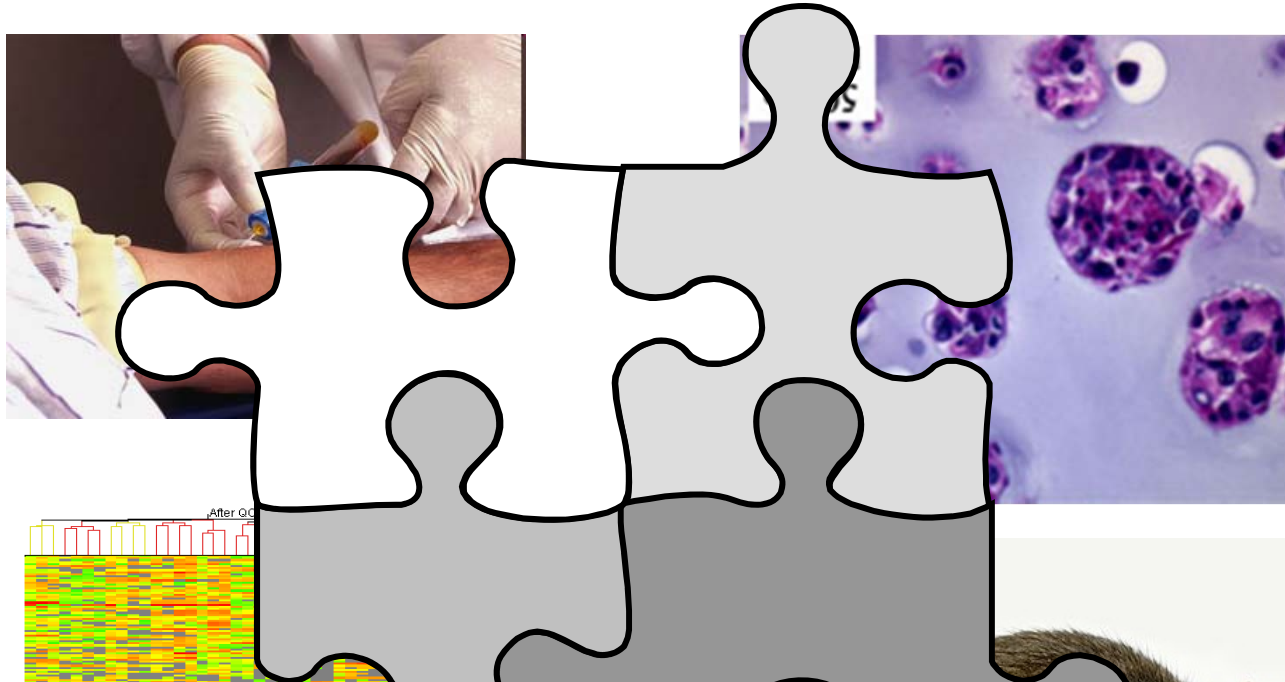




# Innovation GxE molmech



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**First molecular mechanism for GxE in psychiatry**

**Better understanding of pathophysiology of stress-related psychiatric disorders**

**Treatments based on causal mechanisms**



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# Budget

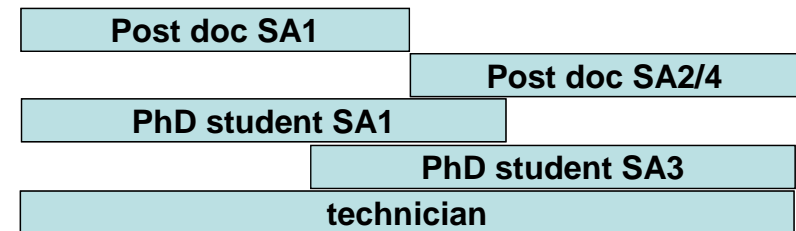


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- **1.045.100 € direct costs**

- **700.000 € personnel**

- 2 postdocs 30 months each
    - 2 PhD students – 36 months each
    - 1 technician – 60 months



- **345.100 € supplies and others**

- DNA methylation and CHIP – 75.000 €
    - Genotyping – 60.000 € for 300 Illumina arrays – 20.000 € Sequenom –
    - Gene expression - 35.000 € for Illumina arrays – 9.000 € for RT-PCR
    - Next generation sequencing – 24.600 €
    - General lab supplies, travel, reimbursements, licences