

# Model driven research in Brain Diseases

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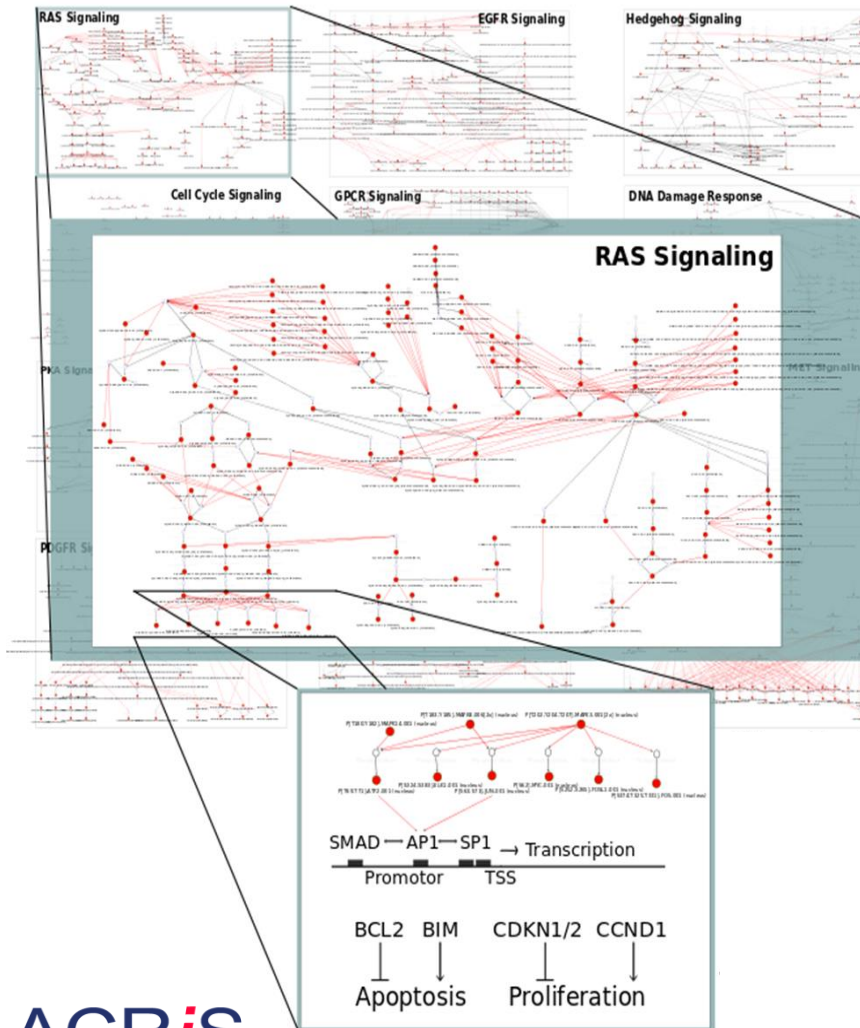
**Alacris Theranostics**



# The case for model-driven research

- current research paradigm - identifies biological mechanisms with simple causality
- evolution generates a ,dark mass' of mechanisms not accessible to current research tools.
- Mechanistic models - compare experimental results and prediction to falsify hypothesis too complex to analyse by currently available strategies

# ModCell™ - a generic mechanistic model of cellular signalling transduction



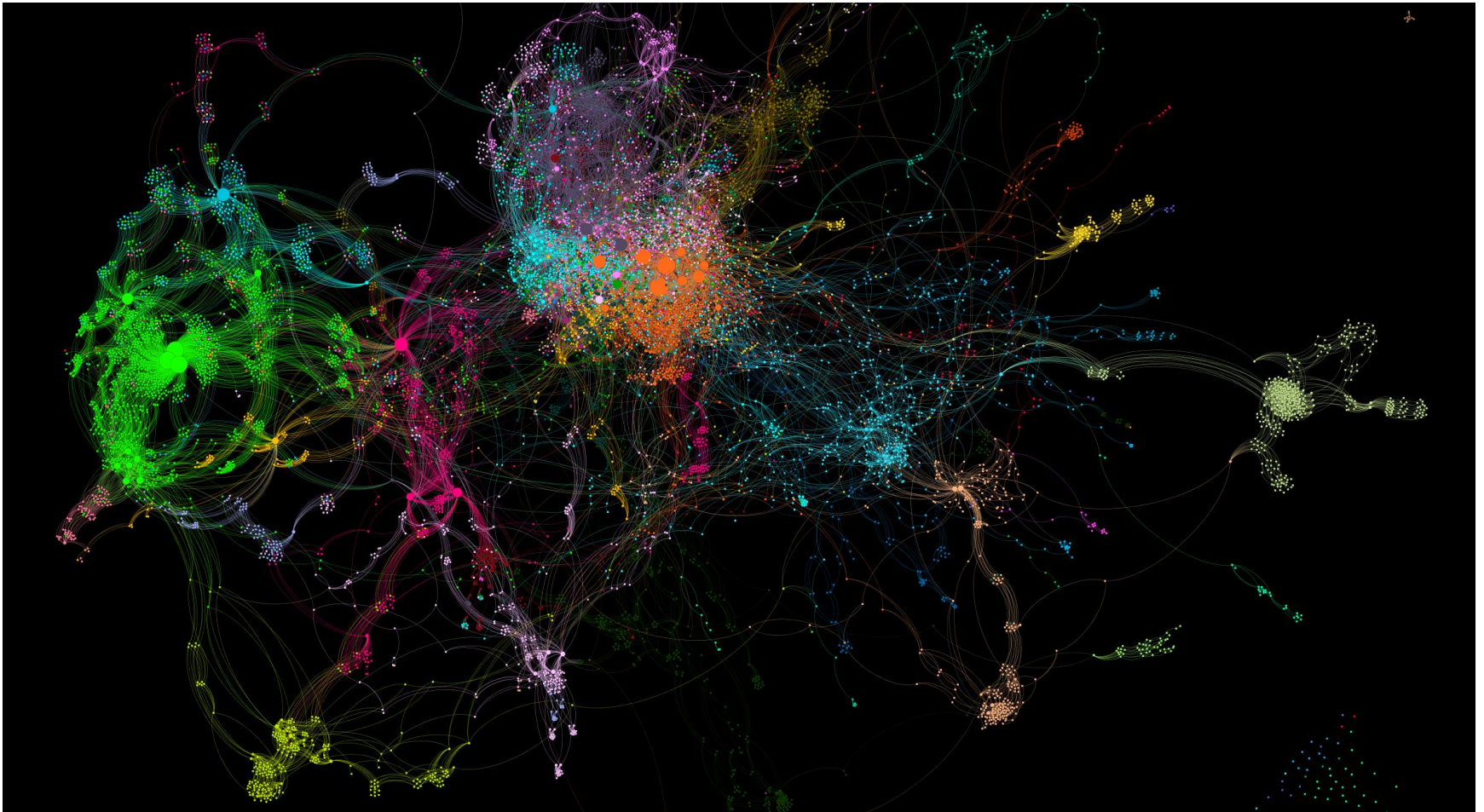
- 50 signalling pathways
- 20,000 reactions
- 800 genes
- 300 targeted drugs

Cancer pathways include:

RTK signaling  
 HEDGEHOG  
 NOTCH  
 WNT  
 TGFB signaling  
 Cytokine signaling  
 Death receptor signaling  
 GPCR/Hormone signaling  
 Ephrin signaling

**Wierling et al., 2015**  
**PMID:26464088**

# Human signalling pathways



# We need samples for molecular analyses

## Fresh human samples

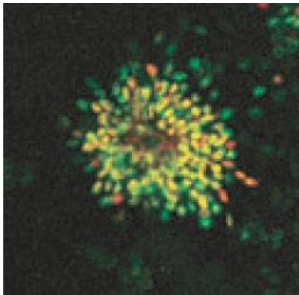
Deep brain stimulation-associated brain tissue imprints: a new *in vivo* approach to biological research in human Parkinsons disease

Affif Zaccaria, Ali Bouamrani, Stephan Chabardès, Michèle El Atifi, Eric Seigneuret, Johannes A. Lohrbus, Michel Dubois-Dauphin and Pierre R. Burkhard

# Surrogate brain tissue: Diverse Methods to Generate Brain Organoids

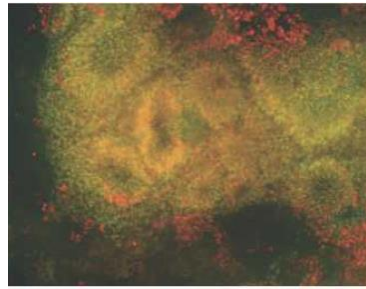
Watanabe et al., 2005

Dkk-1 ; Lefty-1



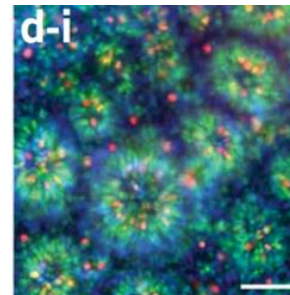
Elkabatz et al., 2008

Nog



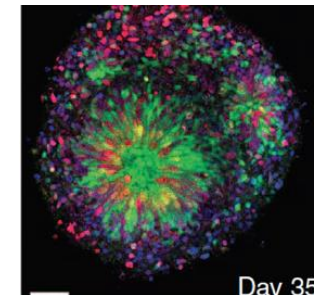
Chambers et al., 2009

SB431542; Nog

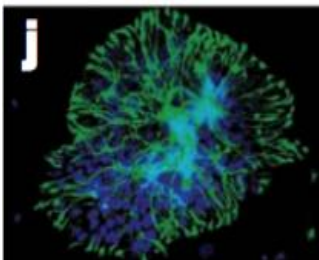


Edri et al., 2015

Nog; LDN; SB431542

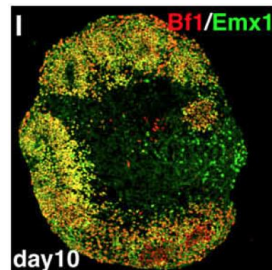


Gaspard et al., 2008  
Intrinsic + Cyclop.



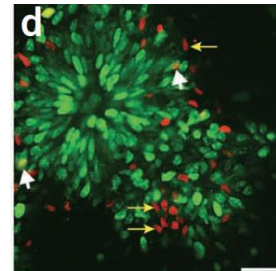
Eiraku et al., 2008

Dkk-1; Lefty-1



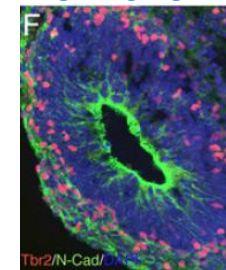
Shi et al., 2012

DM/Nog; SB431542  
FGF2



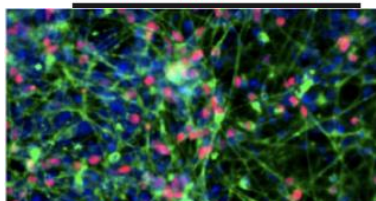
Mariani et al., 2012

Dkk-1; 1BMPRIA-Fc  
SB431542



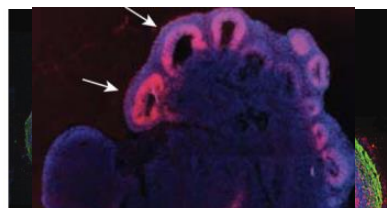
Pascual et al., 2013

LDN; DM; SB431542; FGF-i



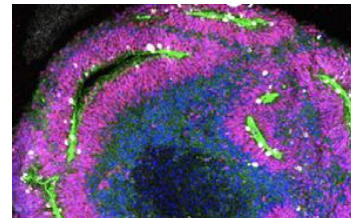
Lancaster et al., 2013

Intrinsic (ICIR)



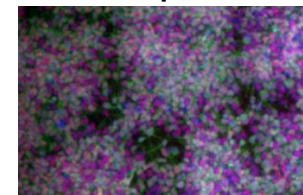
Bednarek et al., 2013

SB; IWRe; SB431542



Maroof et al., 2013

XAV; LDN; SB431542;  
Purmorphamine



# Genomics dominates “omics”

One NGS run generates as much information as one million runs on the sequencers used 10 years ago

1990-2000



2006-2012

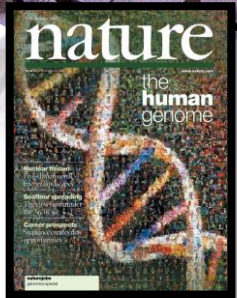


GAII:  
Hiseq machines  
1 human genome/few days

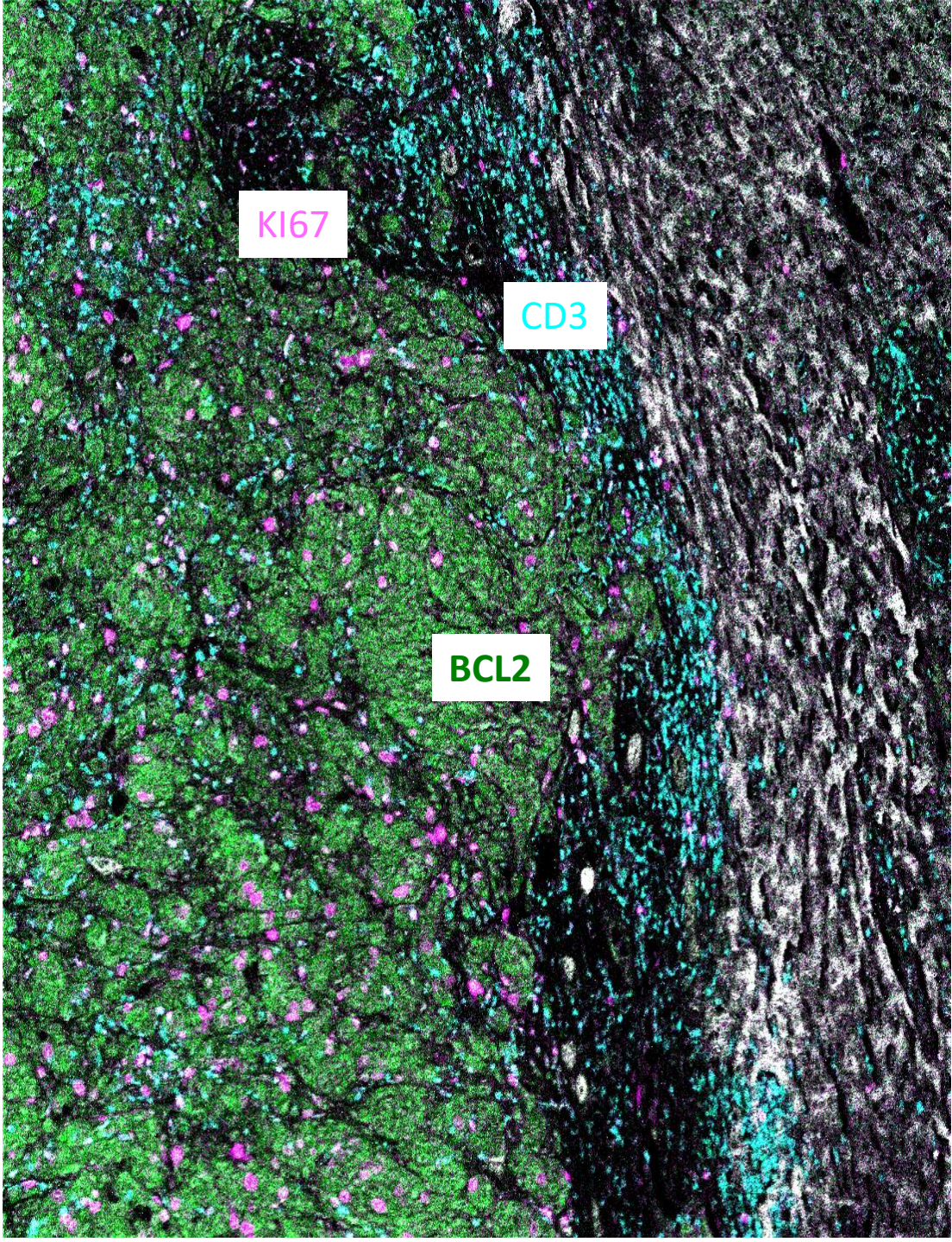
2017



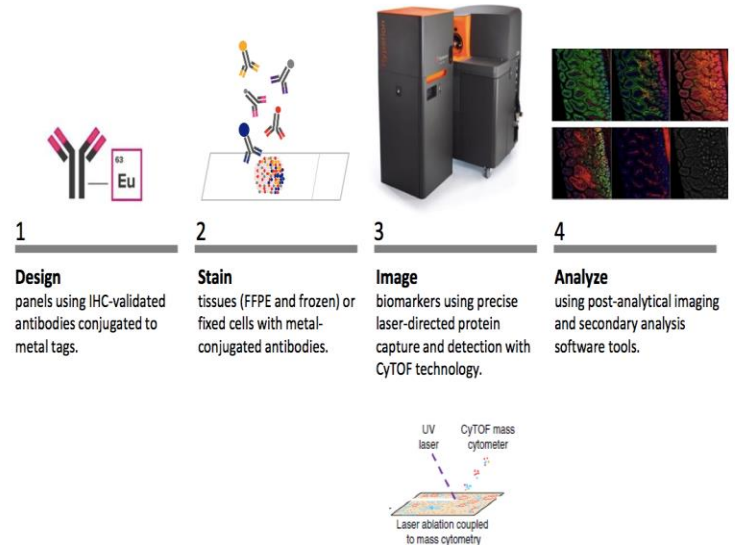
Novaseq6000  
60 genomes in parallel



Human genome project  
1 human genome/ 13 years

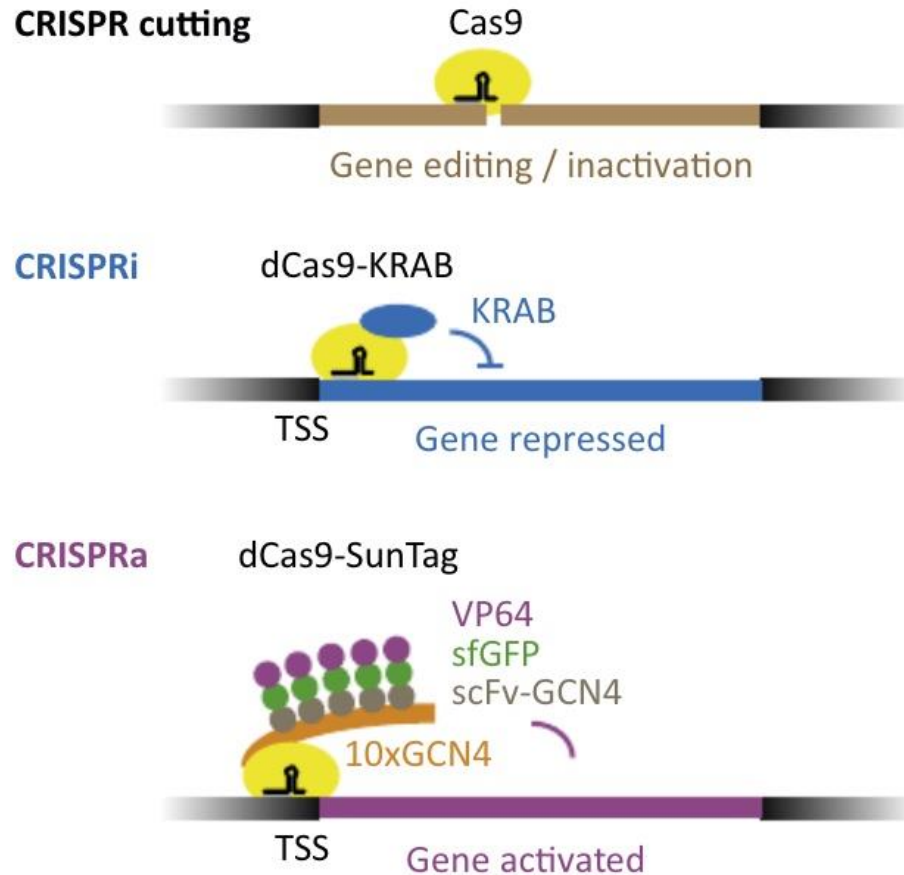


Resolving RNAseq data spatially at the protein level by  
Imaging Mass Cytometry (IMC)  
40 Ab in one experiment

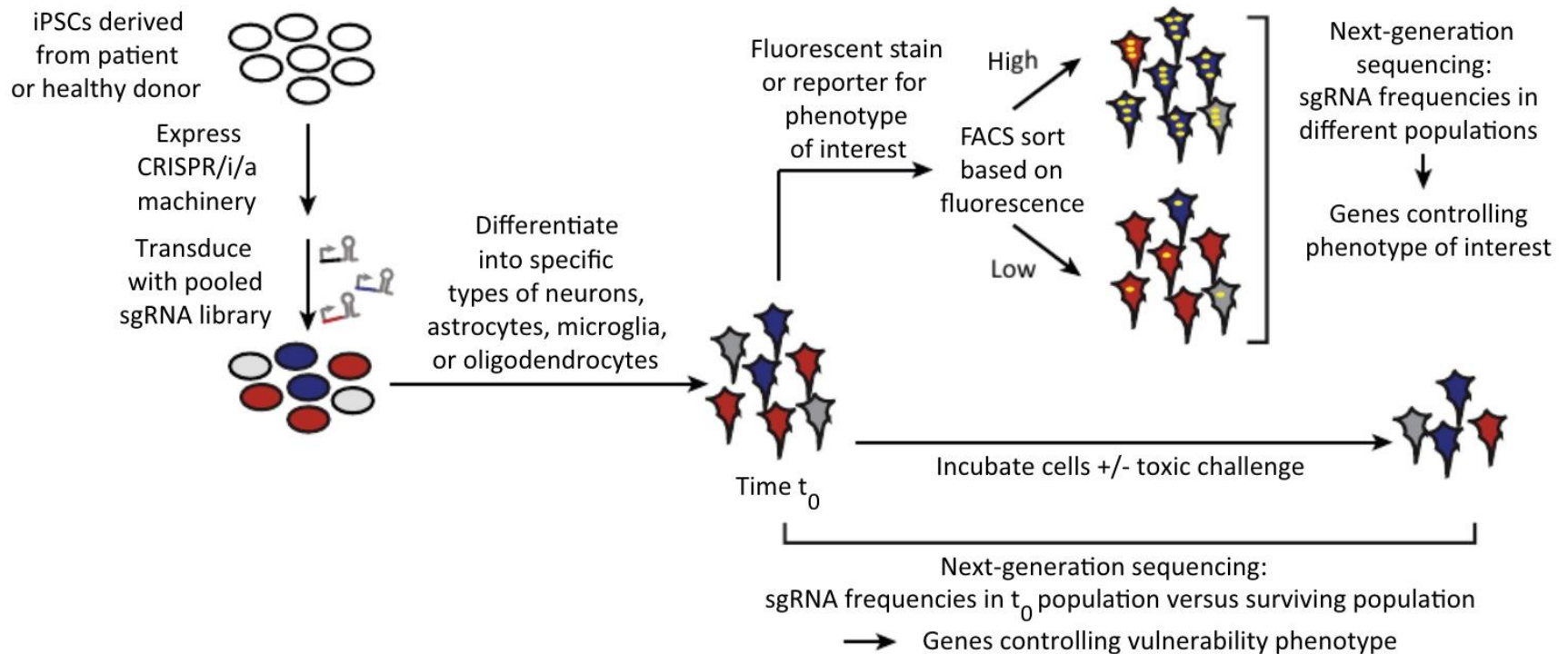


M.-L. Yaspo, Unpublished

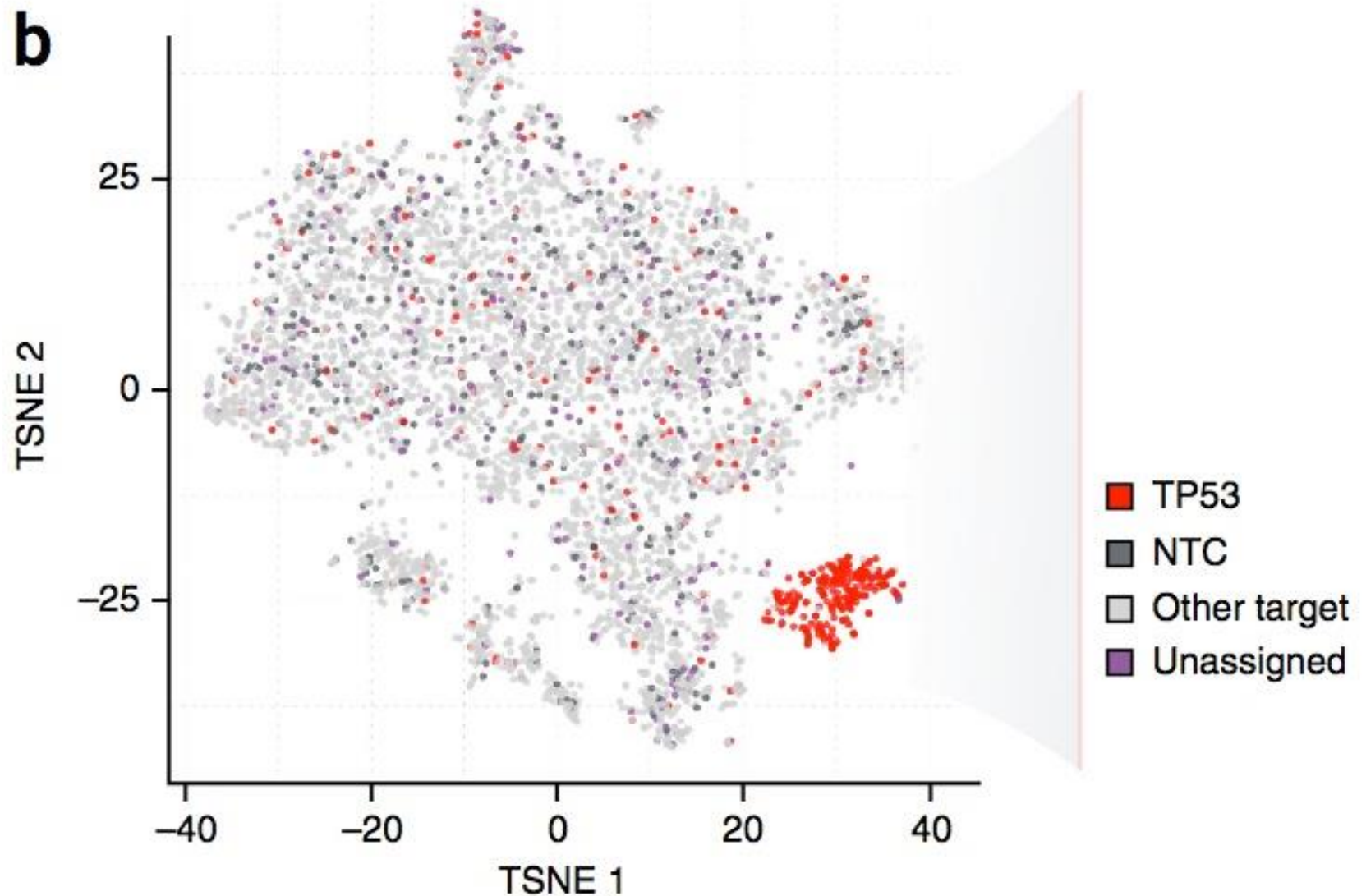
# CRISPR variants



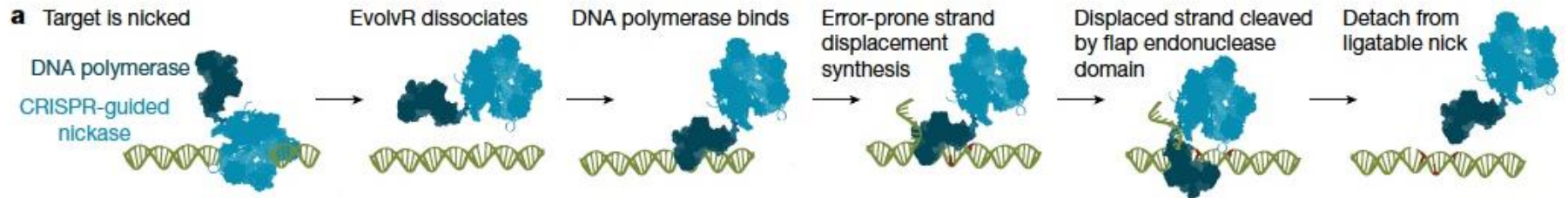
# CRISPR-phenotype screens



# CrispR Droplet sequencing: CROPseq (Christoph Bock)

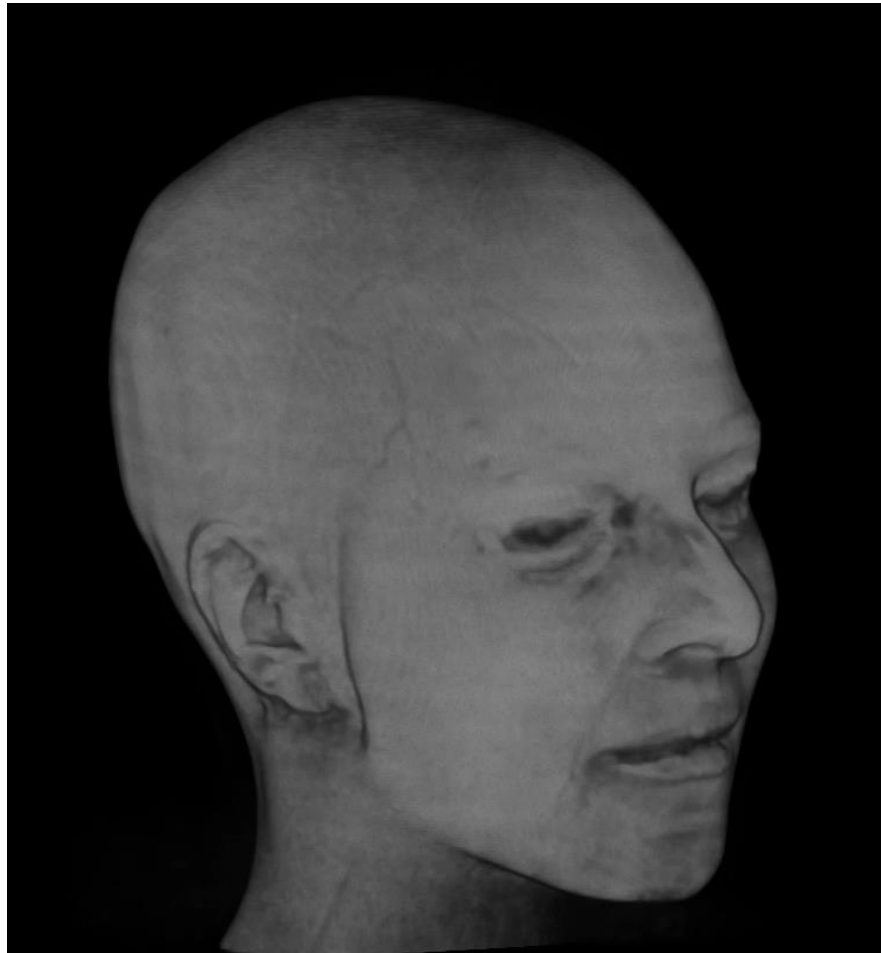


# Lineage tracing: EvolvR



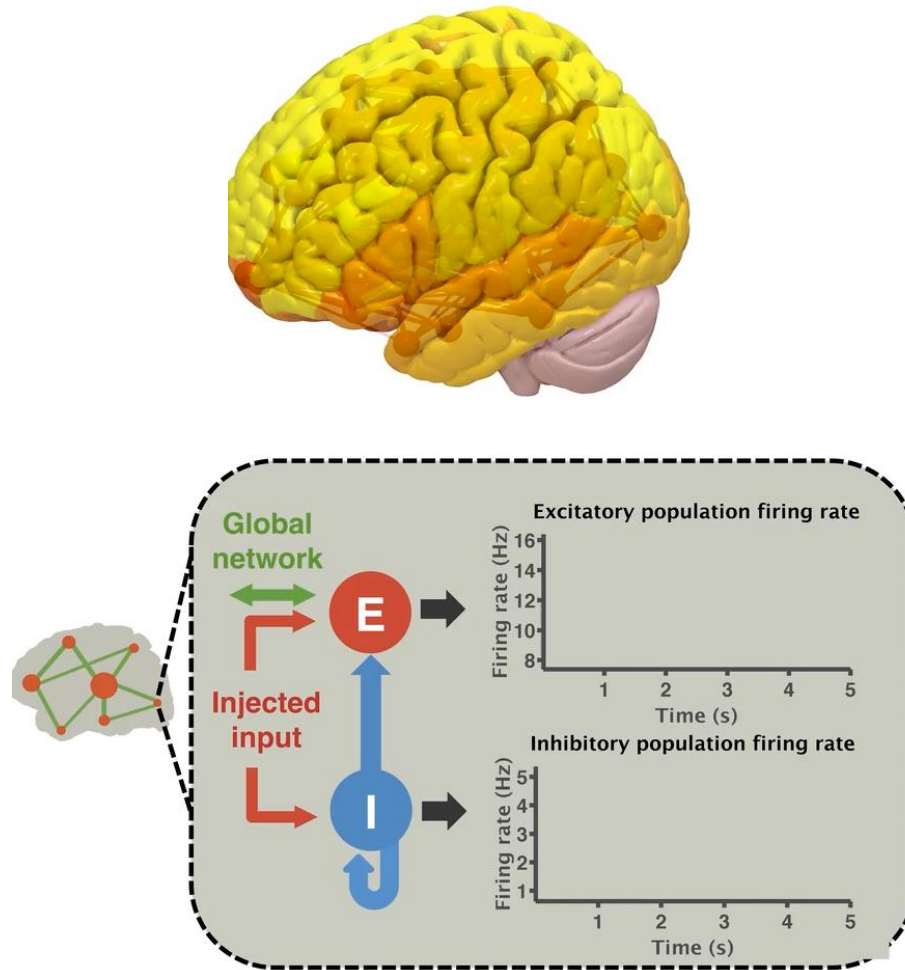
"Brain, New Approach to Brain Diseases"  
Workshop 21st November 2018

# Brain network dynamics simulations



Schirner, Rothmeier, Jirsa, McIntosh, Ritter 2015 **Neuroimage** An automated pipeline for constructing personalized virtual brains from multimodal neuroimaging data

# Inferring unobservable mechanisms through personalized simulation



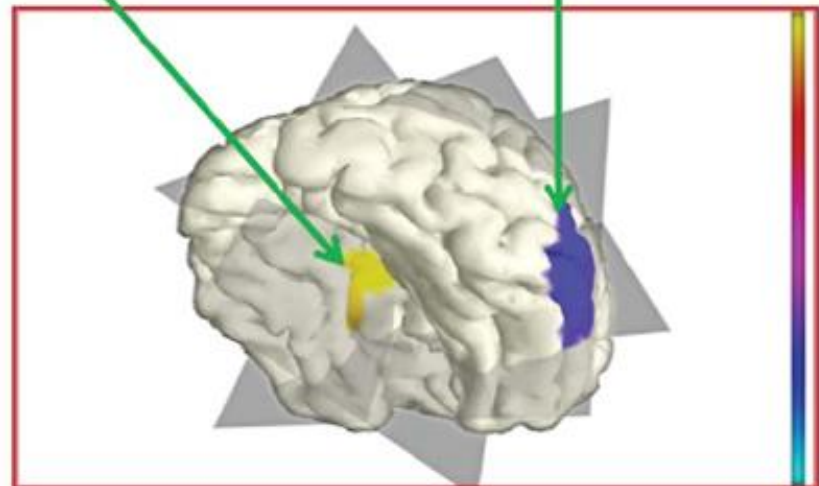
Schirner, McIntosh, Jirsa, Deco, Ritter 2018 **eLife**

Inferring multi-scale mechanisms using brain network modelling

# Linking systems biology and computational neuroscience

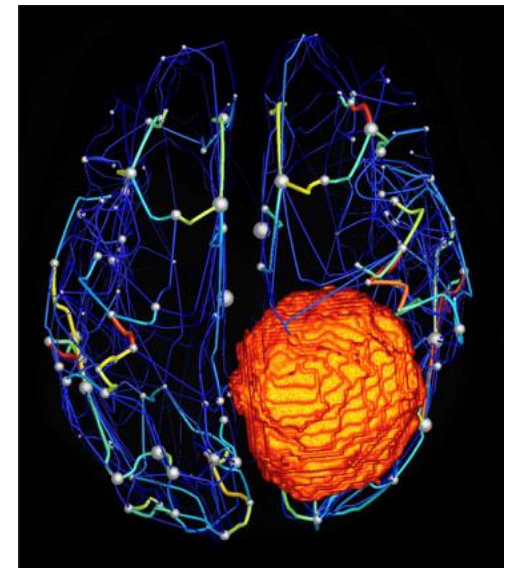
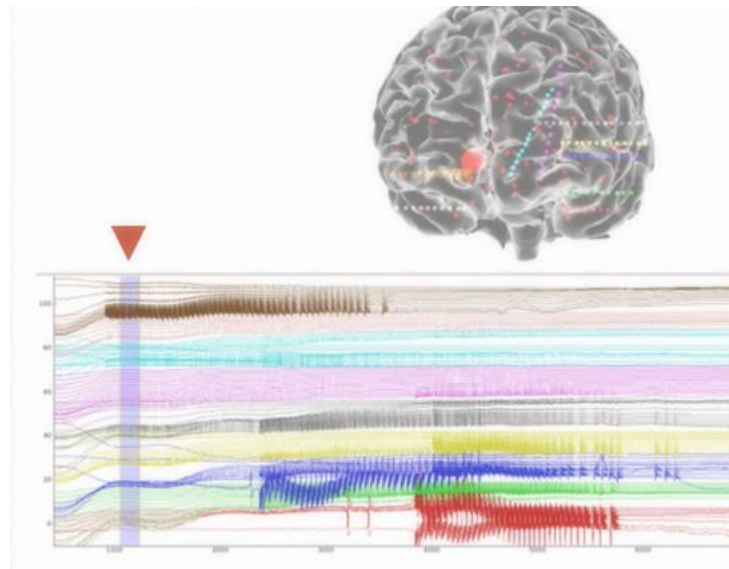
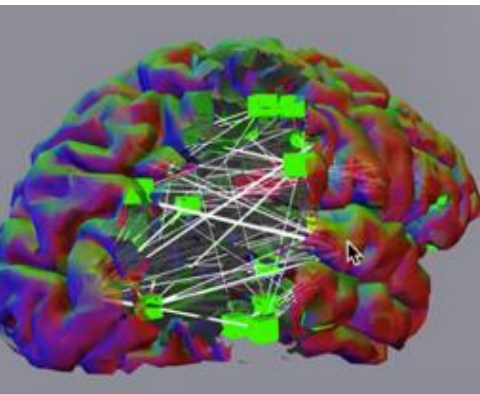
PATHWAYS
Mitochondrial Biogenesis Pathway ↓
Energy Metabolism ↓
Nogo-A to Nogo-66 receptor (NgR) Pathway ↑
Leptin Signaling ↓
Glucose Metabolism ↓
PI3K/Mtor Pathway ↓
JAK/STAT Pathway ↓
ERK Pathway ↓
p38 MAPK Pathway ↑
APP Processing ↑ - Increased neuritic "branching"
Tau Phosphorylation - Tau aggregation
Oxidative stress pathway ↑
Endocytosis pathway - Downregulation of flotillin-2
Glucose Metabolism ↓
Glutamatergic pathway ↑

PATHWAYS
Glucose Metabolism ↓



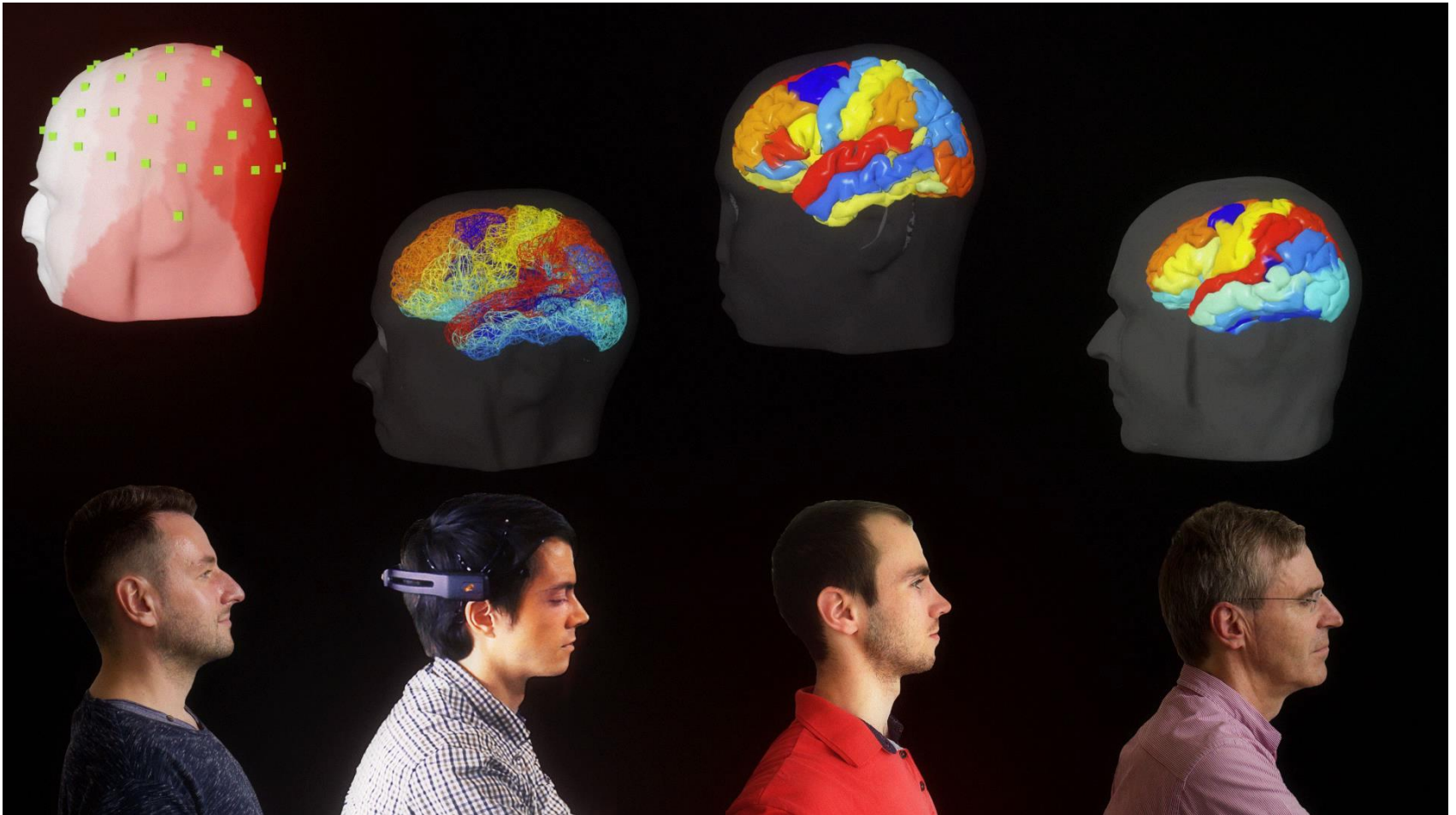
Iyappan et al. 2016 J Alzheimer's Disease. Towards a Pathway Inventory of the Human Brain for Modeling Disease Mechanisms Underlying Neurodegeneration

# Applications in Stroke, Epilepsy, Tumors, Dementia, Schizophrenia...



E.g. Proix et al. 2017 Brain ; Jirsa et al. 2014 Brain; Zimmermann et al. 2018 Neuroimage Clinical; Aerts et al. eNeuro 2018

# 100 000 virtual brains from uk biobank



# Examples

- Parkinson's disease: models based on –omics analysis of cells recovered during therapeutic deep brain stimulation
- MS: deep immune status, modelling the immune system, analysis of monozygotic twins with/without MS
- Migraine: GWAS modelling, brain simulation (Petra Ritter, Charité)
- .....

# FET-Flagship project application

## [www.digitwins.org](http://www.digitwins.org)

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# DigiTwins

## DIGITAL TWINS FOR BETTER HEALTH

Better diagnosis – Better care – Better life



# Without DigiTwins ([www.digitwins.org](http://www.digitwins.org)), we will, over the next framework program

- Spend €10 trillion on healthcare
- Spend ~€2 trillion on drugs, to which the individual patients do not respond, and their consequences
- Have the equivalent of the population of Milan die of adverse drug reaction
- Come 7 years closer to the implosion of the European healthcare system
- Make little progress on biological mechanism with complex causality
- Save €1 bn over 10 years, the equivalent of the amount we spend in healthcare every 5 hours (and probably waste every 10 hours).

If you think this could be relevant to Europe and the European Citizens, please mail ([lehrach@molgen.mpg.de](mailto:lehrach@molgen.mpg.de)) or call (+491723839194) me (and tell your colleagues).