NIMH
National Institute of Mental Health

New Treatments for Neurodevelopmental Disorders

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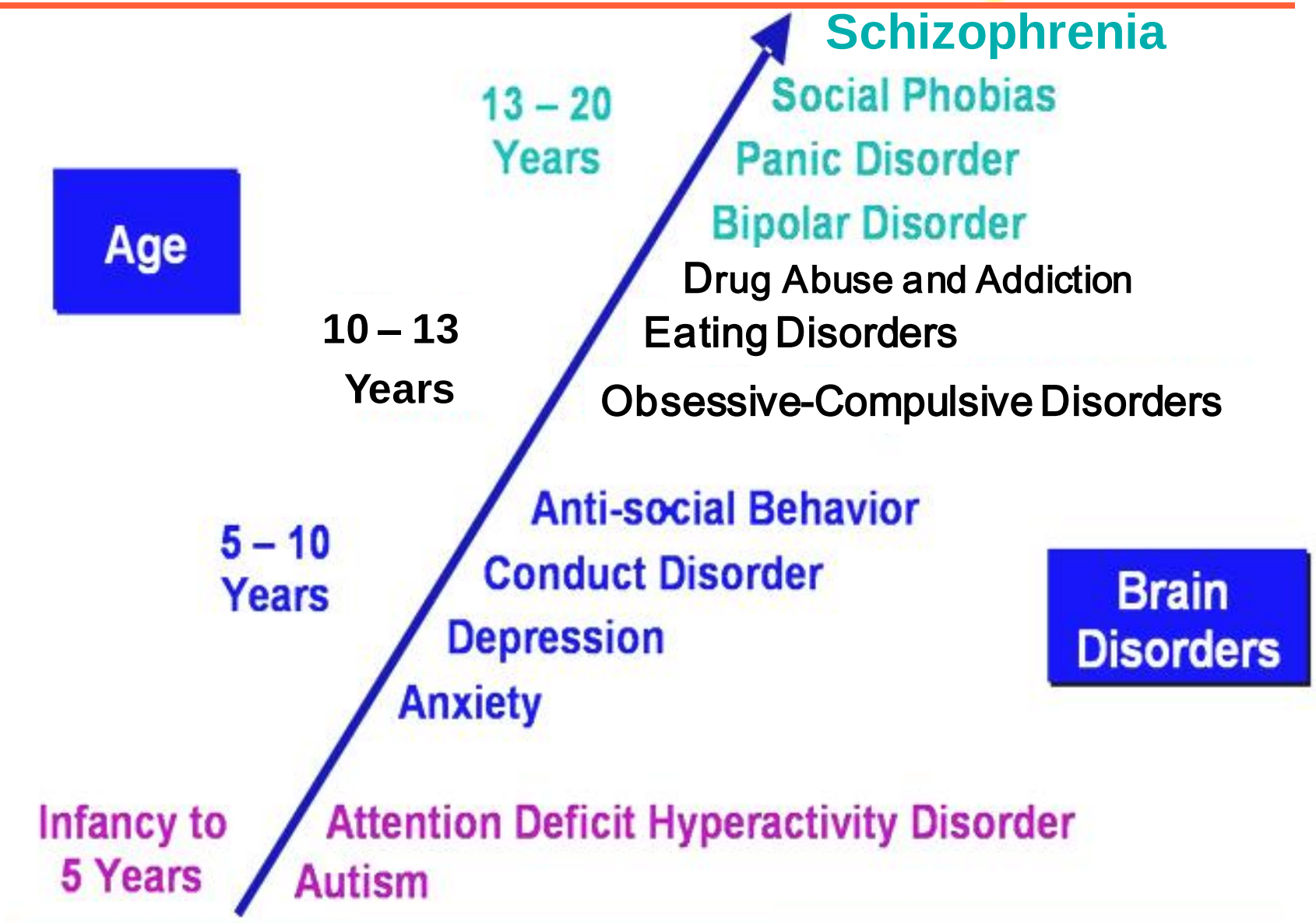
Director, NIMH

February 23, 2012

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NATIONAL INSTITUTES OF HEALTH

Mental Disorders are Developmental



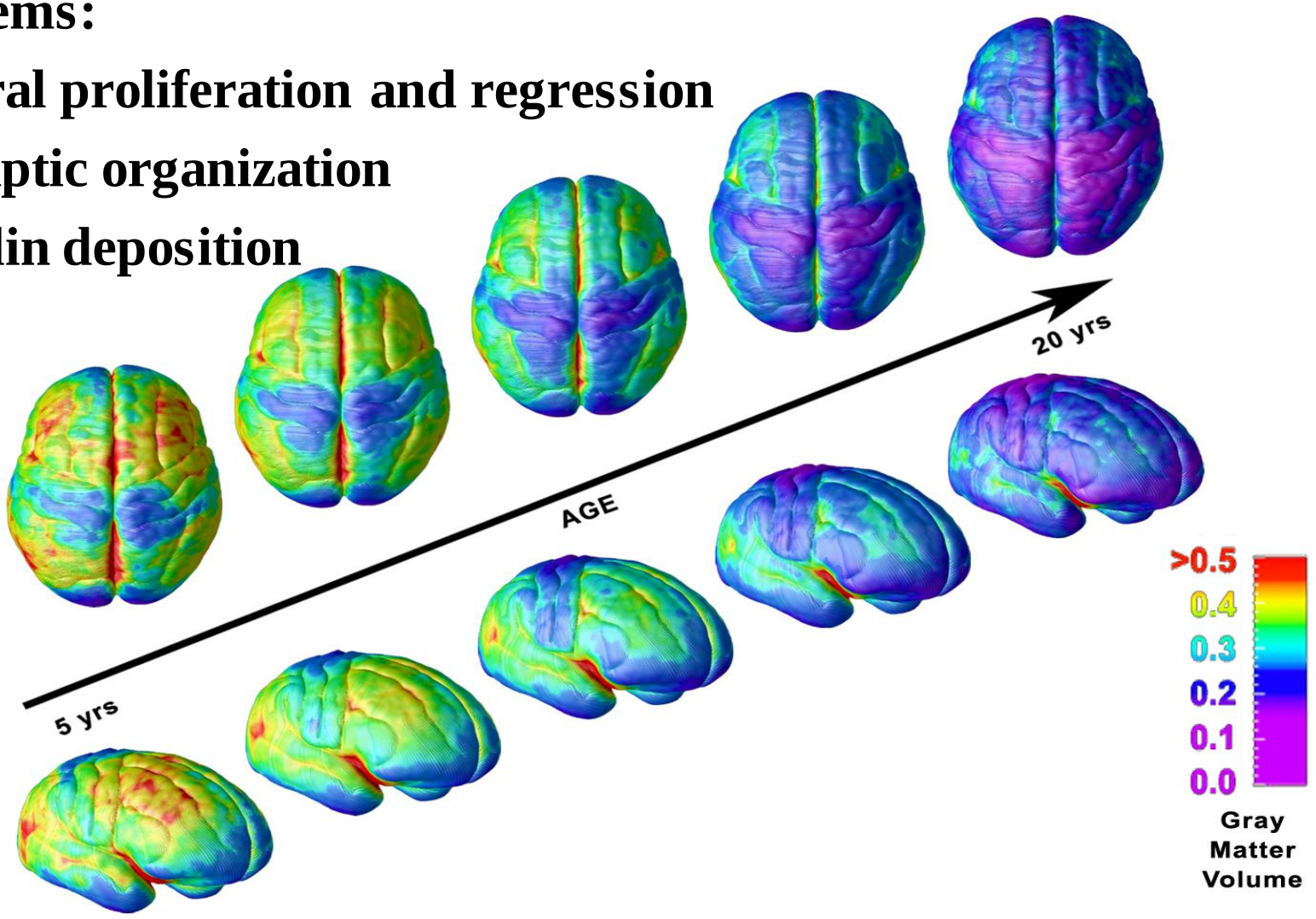
Development: What is it?

Systems:

Neural proliferation and regression

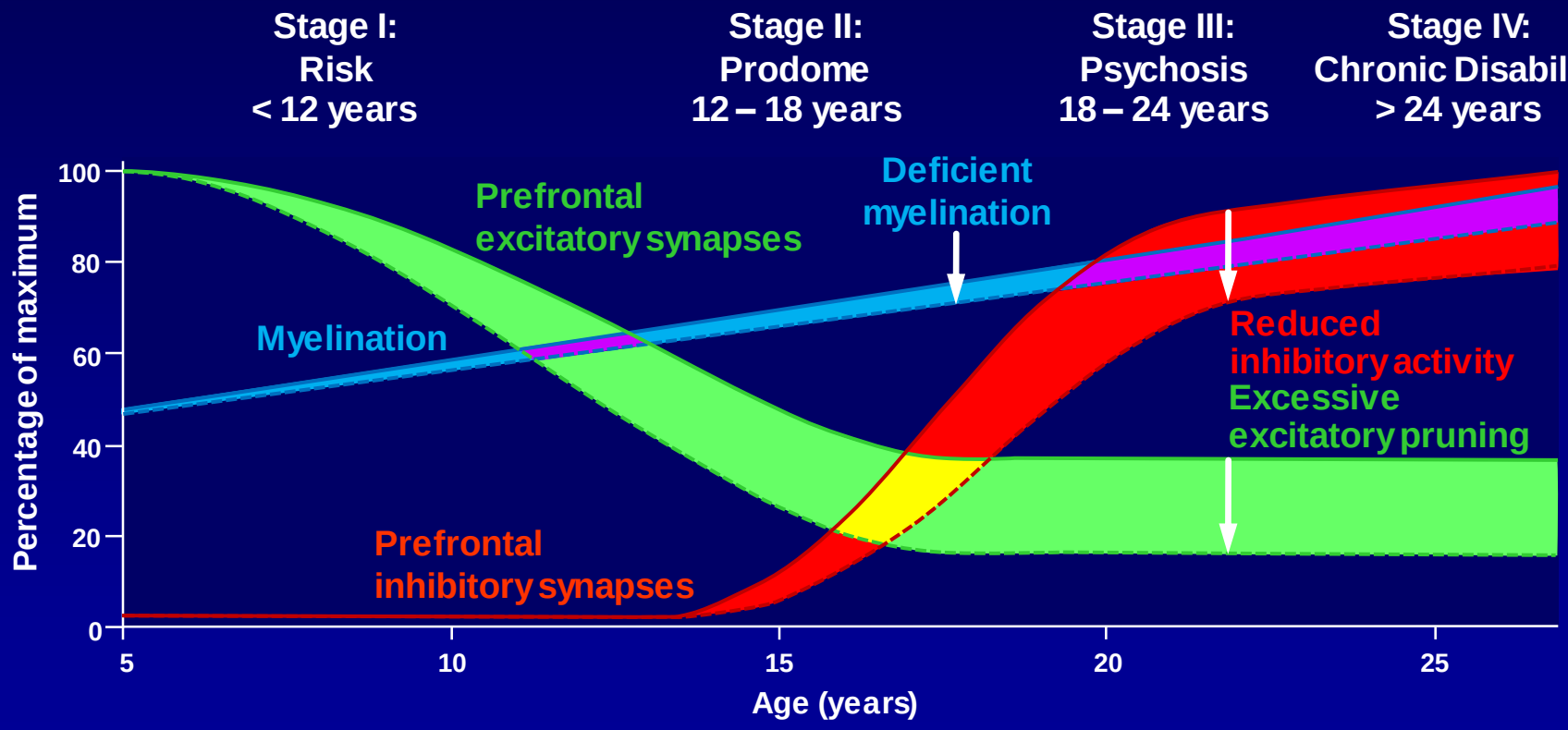
Synaptic organization

Myelin deposition



Source: J Giedd, NIMH

Altered Cortical Development in Schizophrenia: Timing and Targets for Preemptive and Personalized Interventions

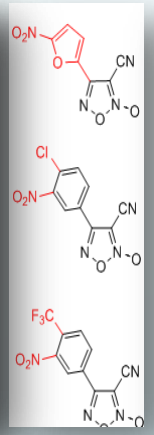


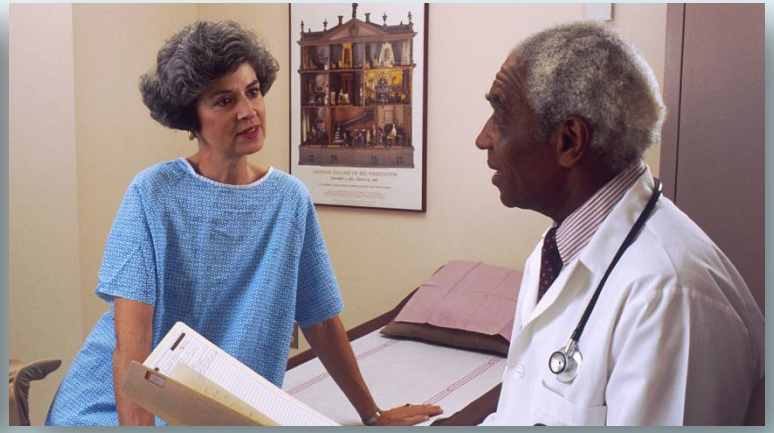
Adapted from
Insel, *Nature*, 2010

Treatment Development for Children

- Biomarkers for early detection
- Preemptive interventions that are stage specific
- Trials that are developmentally informed
- High margin of safety for interventions

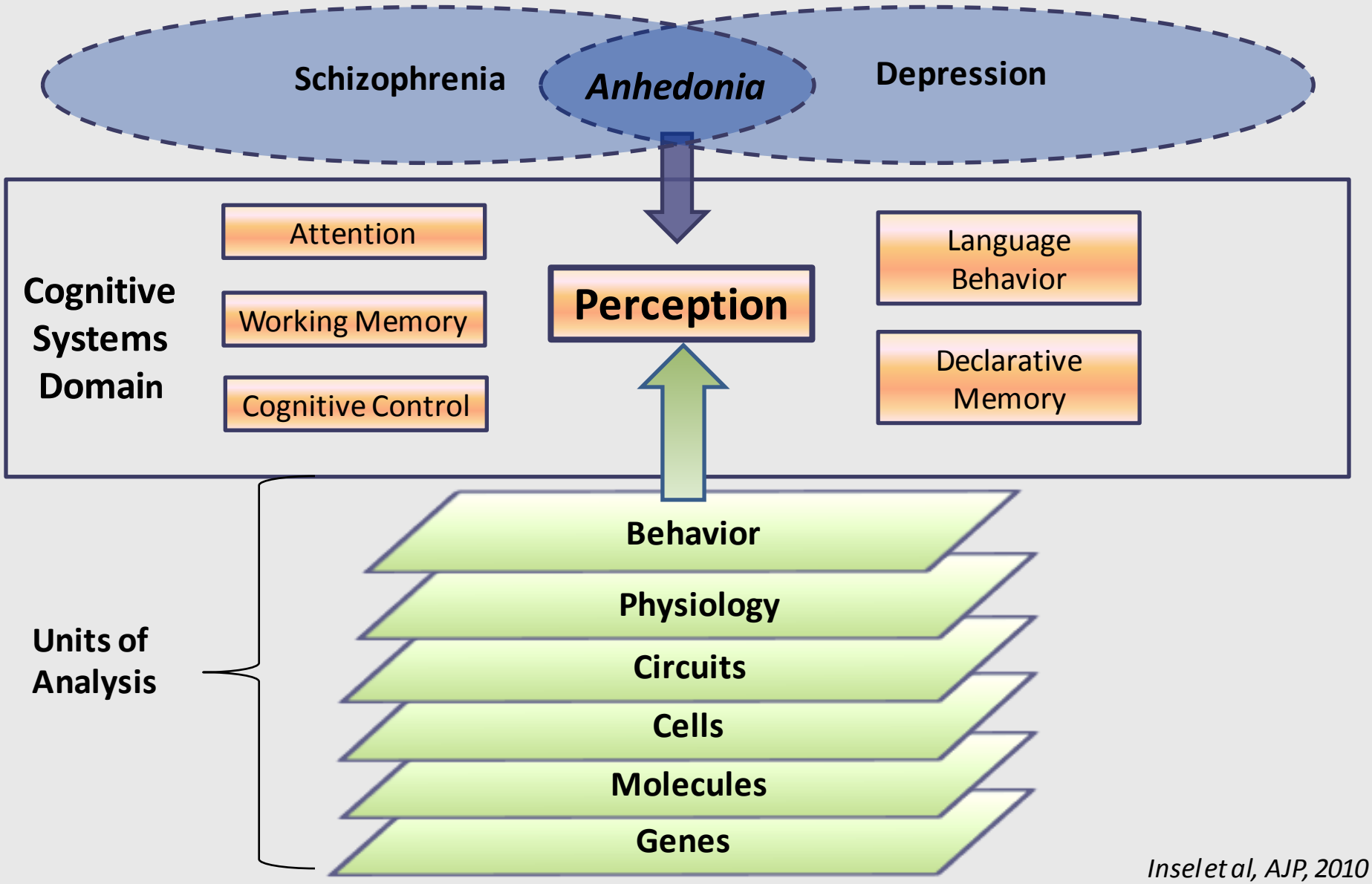
Advancing Translational Science: The Pipeline





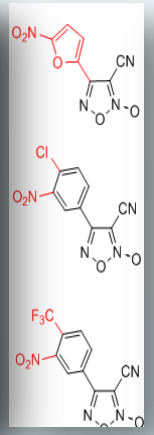
Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

RDoC Research Domain Criteria



Insel et al, AJP, 2010

Advancing Translational Science: The Pipeline



Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

Molecular Target: BCL11a

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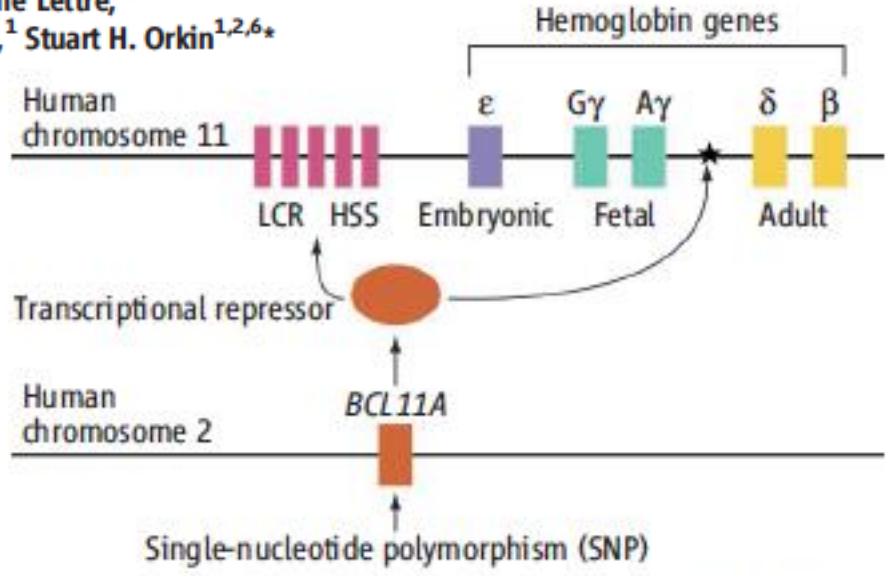
Human Fetal Hemoglobin Expression Is Regulated by the Developmental Stage-Specific Repressor *BCL11A*

Vijay G. Sankaran,[1,2] Tobias F. Menne,[1] Jian Xu,[1] Thomas E. Akie,[1] Guillaume Lettre,[3,4] Ben Van Handel,[5] Hanna K. A. Mikkola,[5] Joel N. Hirschhorn,[3,4] Alan B. Cantor,[1] Stuart H. Orkin[1,2,6]*

Science
AAAS

- Mutant adult Hgb cannot bind O2
- Fetal Hgb spared
- Fetal Hgb reduced postnatally

Will blockade of a repressor of fetal Hgb lead to an effective treatment for Sickle Cell Anemia?



Expression		*BCL11A* SNP
Fetal hemoglobin	*BCL11A*	
Low	High	GG (homozygous)
High	Low	AA (homozygous)

Transformative Technologies – iPS cells

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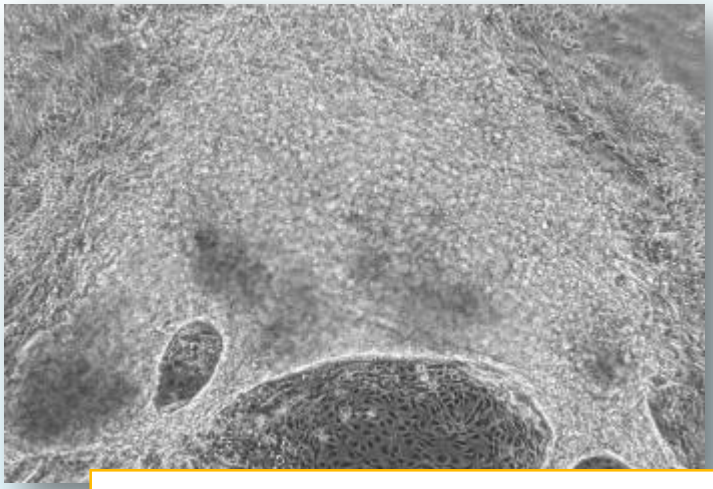

Science

AAAS

Science **318**, 1917 (2007)

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,[1,2]* Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5]*

Cell *131*, 861–872, November 30, 2007 ©2007 Elsevier Inc.

Cell

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
[3]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
[4]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

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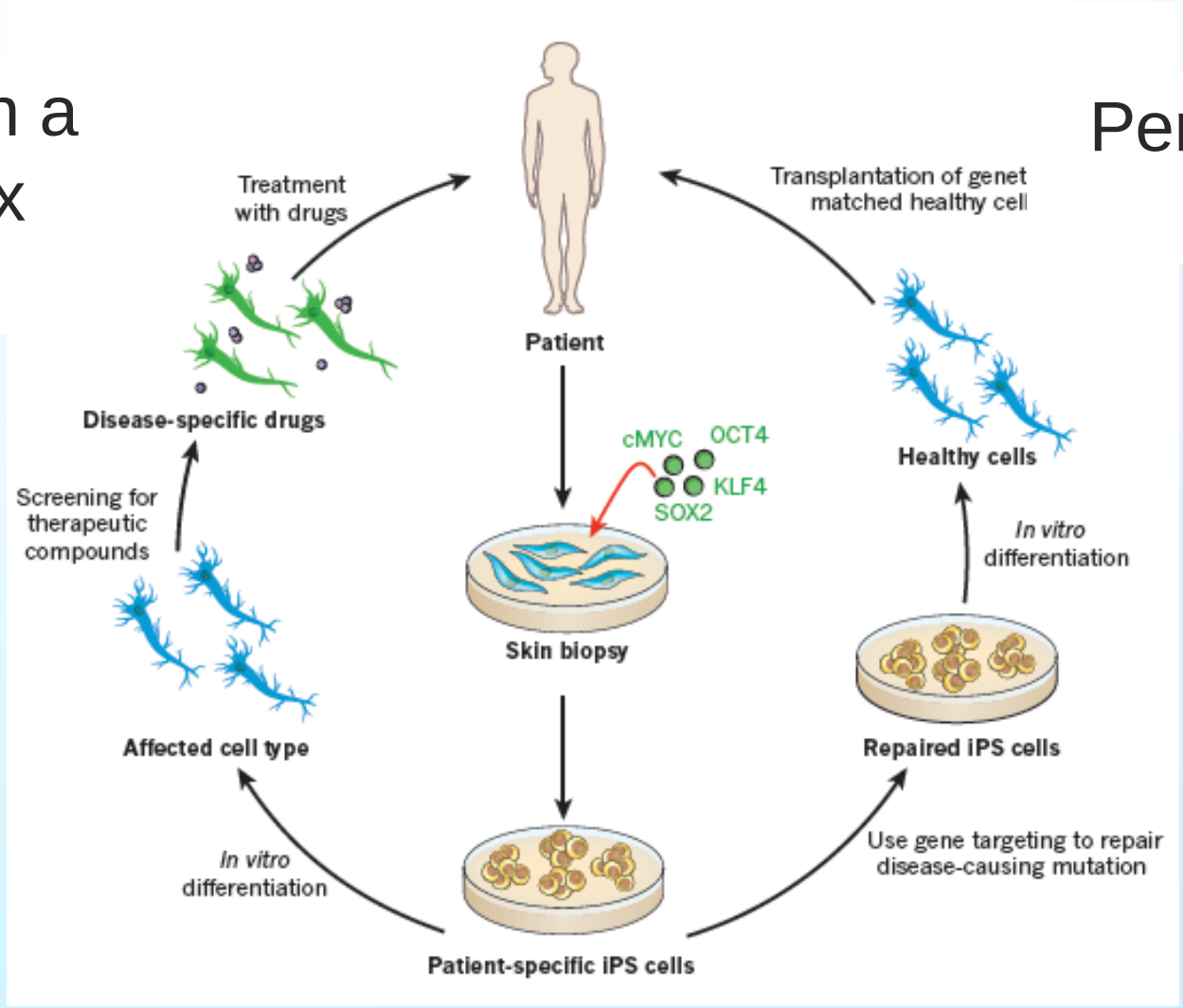
Transformative Technologies – iPS cells

Disease in a dish for Rx screening



Personalized cell Rx

Nature, Jan 19, 2012 vol 481

iPS Models of Disease

- > 45 diseases to date
  - Neurological
  - Hematological
  - Metabolic
  - Cardiovascular
  - Primary Immunodeficiency
  - Other

Individuals with copy number variants:
Schizophrenia (VCFS)
Autism (Rett, Timothy Syndrome, Fragile X)

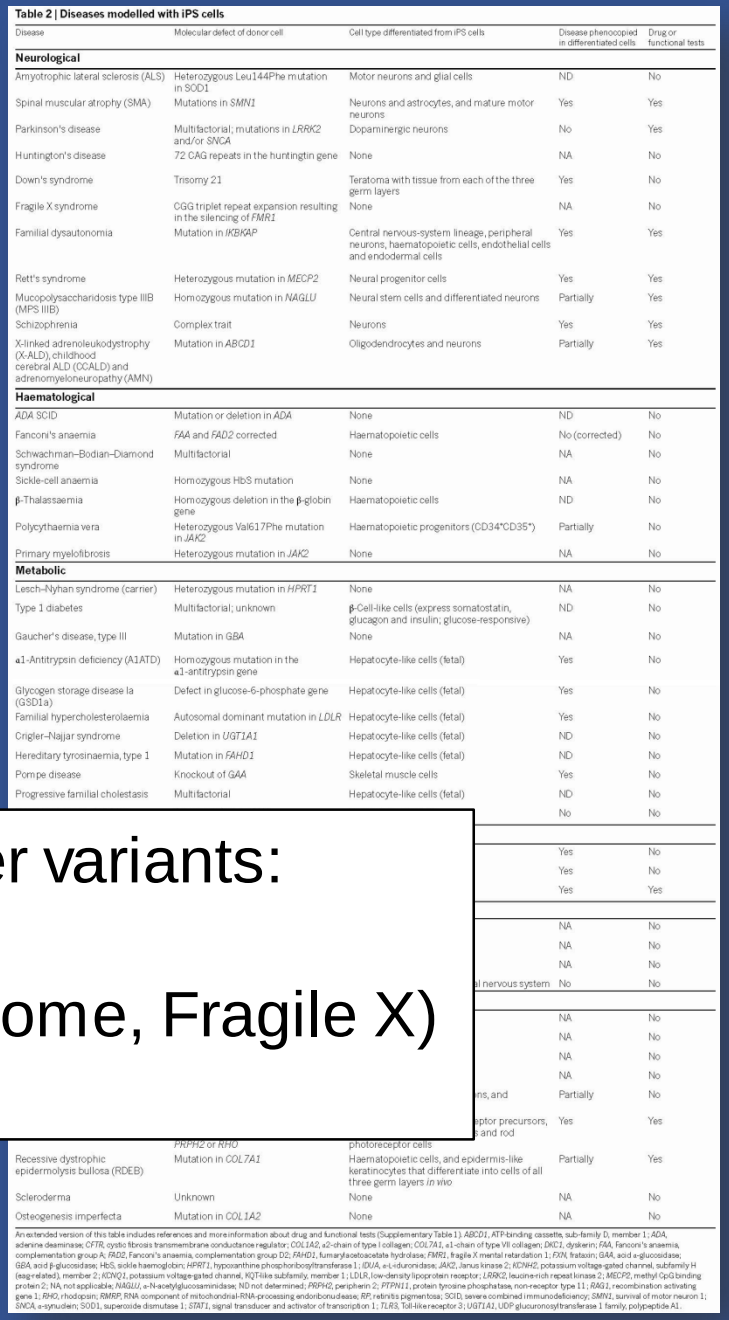


Table 2 | Diseases modelled with iPS cells

Disease	Molecular defect of donor cell	Cell type differentiated from iPS cells	Disease phenocopied in differentiated cells	Drug or functional tests
Neurological				
Amyotrophic lateral sclerosis (ALS)	Heterozygous Leu144Phe mutation in SOD1	Motor neurons and glial cells	ND	No
Spinal muscular atrophy (SMA)	Mutations in *SMN1*	Neurons and astrocytes, and mature motor neurons	Yes	Yes
Parkinson's disease	Multifactorial; mutations in *LRRK2* and/or *SNCA*	Dopaminergic neurons	No	Yes
Huntington's disease	72 CAG repeats in the huntingtin gene	None	NA	No
Down's syndrome	Trisomy 21	Teratoma with tissue from each of the three germ layers	Yes	No
Fragile X syndrome	CGG triplet repeat expansion resulting in the silencing of *FMR1*	None	NA	No
Familial dysautonomia	Mutation in *IKBKAP*	Central nervous-system lineage, peripheral neurons, haematopoietic cells, endothelial cells and endodermal cells	Yes	Yes
Rett's syndrome	Heterozygous mutation in *MECP2*	Neural progenitor cells	Yes	Yes
Mucopolysaccharidosis type IIIB (MPS IIIB)	Homozygous mutation in *NAGLU*	Neural stem cells and differentiated neurons	Partially	Yes
Schizophrenia	Complex trait	Neurons	Yes	Yes
X-linked adrenoleukodystrophy (X-ALD), childhood cerebral ALD (CCALD) and adrenomyeloneuropathy (AMN)	Mutation in *ABCD1*	Oligodendrocytes and neurons	Partially	Yes
Haematological				
ADA SCID	Mutation or deletion in *ADA*	None	ND	No
Fanconi's anaemia	*FAA* and *FAD2* corrected	Haematopoietic cells	No (corrected)	No
Schwachman–Bodian–Diamond syndrome	Multifactorial	None	NA	No
Sickle-cell anaemia	Homozygous HbS mutation	None	NA	No
β-Thalassaemia	Homozygous deletion in the β-globin gene	Haematopoietic cells	ND	No
Polycythaemia vera	Heterozygous Val617Phe mutation in *JAK2*	Haematopoietic progenitors (CD34⁺CD35⁺)	Partially	No
Primary myelofibrosis	Heterozygous mutation in *JAK2*	None	NA	No
Metabolic				
Lesch–Nyhan syndrome (carrier)	Heterozygous mutation in *HPRT1*	None	NA	No
Type 1 diabetes	Multifactorial; unknown	β-Cell-like cells (express somatostatin, glucagon and insulin; glucose-responsive)	ND	No
Gaucher's disease, type III	Mutation in *GBA*	None	NA	No
α1-Antitrypsin deficiency (A1ATD)	Homozygous mutation in the α1-antitrypsin gene	Hepatocyte-like cells (fetal)	Yes	No
Glycogen storage disease Ia (GSD1a)	Defect in glucose-6-phosphate gene	Hepatocyte-like cells (fetal)	Yes	No
Familial hypercholesterolaemia	Autosomal dominant mutation in *LDLR*	Hepatocyte-like cells (fetal)	Yes	No
Crigler–Najjar syndrome	Deletion in *UGT1A1*	Hepatocyte-like cells (fetal)	ND	No
Hereditary tyrosinaemia, type 1	Mutation in *FAHD1*	Hepatocyte-like cells (fetal)	ND	No
Pompe disease	Knockout of *GAA*	Skeletal muscle cells	Yes	No
Progressive familial cholestasis	Multifactorial	Hepatocyte-like cells (fetal)	ND	No
			No	No
			Yes	No
			Yes	No
			Yes	Yes
			NA	No
			NA	No
			NA	No
			l nervous system	No
			NA	No
			NA	No
			NA	No
			NA	No
			ns, and	Partially
			eptor precursors, s and rod	Yes
	PRPH2 or *RHO*	photoreceptor cells		
Recessive dystrophic epidermolysis bullosa (RDEB)	Mutation in *COL7A1*	Haematopoietic cells, and epidermis-like keratinocytes that differentiate into cells of all three germ layers *in vivo*	Partially	Yes
Scleroderma	Unknown	None	NA	No
Osteogenesis imperfecta	Mutation in *COL1A2*	None	NA	No

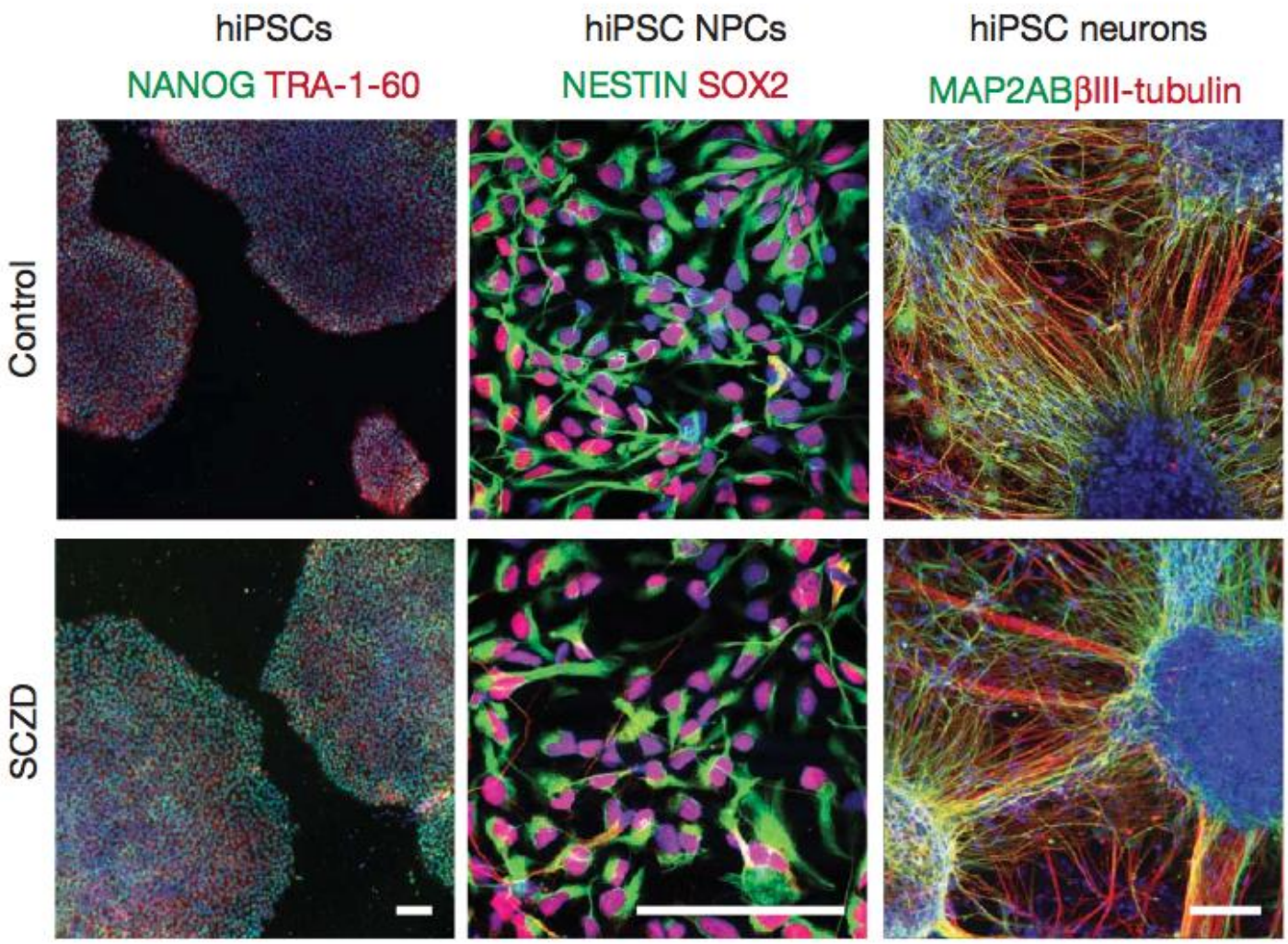
An extended version of this table includes references and more information about drug and functional tests (Supplementary Table 1). *ABCD1*, ATP-binding cassette, sub-family D, member 1; *ADA*, adenine deaminase; *CFTR*, cystic fibrosis transmembrane conductance regulator; *COL1A2*, α2-chain of type I collagen; *COL7A1*, α1-chain of type VII collagen; *DKC1*, dyskerin; *FAA*, Fanconi's anaemia, complementation group A; *FAD2*, Fanconi's anaemia, complementation group D2; *FAHD1*, fumarylacetoacetate hydrolase; *FMR1*, fragile X mental retardation 1; *FXN*, frataxin; *GAA*, acid α-glucosidase; *GBA*, acid β-glucosidase; HbS, sickle haemoglobin; *HPRT1*, hypoxanthine phosphoribosyltransferase 1; *IDUA*, α-L-iduronidase; *JAK2*, Janus kinase 2; *KCNH2*, potassium voltage-gated channel, subfamily H (eag-related), member 2; *KCNQ1*, potassium voltage-gated channel, KQT-like subfamily, member 1; *LDLR*, low-density lipoprotein receptor; *LRRK2*, leucine-rich repeat kinase 2; *MECP2*, methyl CpG binding protein 2; NA, not applicable; *NAGLU*, α-N-acetylglucosaminidase; ND not determined; *PRPH2*, peripherin 2; *PTPN11*, protein tyrosine phosphatase, non-receptor type 11; *RAG1*, recombination activating gene 1; *RHO*, rhodopsin; *RMRP*, RNA component of mitochondrial-RNA-processing endoribonuclease; *RP*, retinitis pigmentosa; SCID, severe combined immunodeficiency; *SMN1*, survival of motor neuron 1; *SNCA*, α-synuclein; SOD1, superoxide dismutase 1; *STAT1*, signal transducer and activator of transcription 1; *TLR3*, Toll-like receptor 3; *UGT1A1*, UDP glucuronosyltransferase 1 family, polypeptide A1.

Nature, Jan 19, 2012 vol 481, 295-96

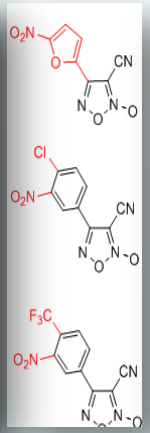
Modelling schizophrenia using human induced pluripotent stem cells

Nature, April, 2011

Kristen J. Brennand[1], Anthony Simone[1]*, Jessica Jou[1]*, Chelsea Gelboin-Burkhart[1]*, Ngoc Tran[1]*, Sarah Sangar[1], Yan Li[1], Yangling Mu[1], Gong Chen[2], Diana Yu[1], Shane McCarthy[3], Jonathan Sebat[4] & Fred H. Gage[1]



Advancing Translational Science: Experimental Medicine



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New Paradigm: Experimental Medicine

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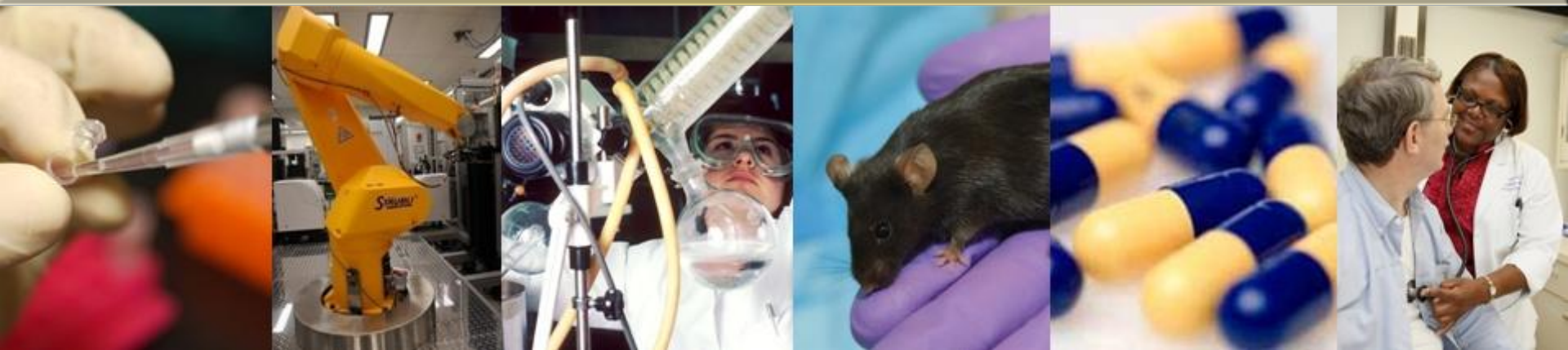
- Move quickly into humans
- Focus on Phase 0 – Phase 2a
- Fail quickly and often
- Target engagement
  - Precompetitive partnerships
  - Share data

National Center for Advancing Translational Sciences (NCATS)

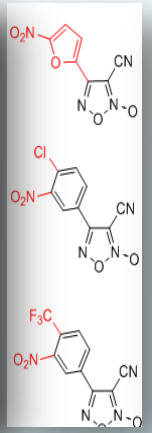
Mission:

To advance the discipline of translational science and catalyze the development, testing, and implementation of novel diagnostics and therapeutics across a wide range of human diseases and conditions.

http://ncats.nih.gov/



Accelerating Rx Development: Rescue and Repurposing



Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

Advancing Translational Science: Repurposing

Repurposing for Mental Disorders

Ketamine
Verapamil
Remicaide
Tamoxifen

Rescuing from Industry

NR2B antagonists
M1-M4 agonists
H3 antagonists

24 June 2011 Vol. 332 no. 603

BIOMEDICINE

NIH's Secondhand Shop for Tried-and-

Although the U.S. National Institutes of Health (NIH) has made waves with a proposed new center aimed at translational research, so far the main innovation has been to put scattered existing programs under the same roof. But this month NIH Director Francis Collins unveiled something fresh: an effort to persuade drug companies to open up their troves of abandoned drugs to academics, who would look for new uses.

University in St. Louis, university researchers have access to a database of 500 Pfizer drugs and failed candidates that they test in animal models.

But NIH officials think there's merit in more systematic effort. One reason is efficiency, NIH Associate Director for Science Policy Amy Patterson explained to the NIH board this month. Although only 1 in 10,000 potential therapeutic compounds will become a drug, the majority fail in late trials because of lack of efficacy, not safety. That means toxicity often isn't a barrier, Patterson said. She cited an estimated success rate of 30% for repurposed drugs. And NIH says that

pound that interests them, they might access a company's proprietary data through service companies.

NIH hopes to complete the model master agreement within 6 to 8 months, Patterson says. The drug rescue and repurposing project will be led by a team at NCATS as "an integral

NIH DRUG REPURPOSING

Drug	Initial Indication	Subsequent Indication
AZT	Antineoplastic	HIV/AIDS
Ceftriaxone	Bacterial infection	Amyotrophic lateral sclerosis
Hydroxyurea	Cancers	Sickle cell anemia
Metformin	Type 2 diabetes	Breast cancer
Pioglitazone	Type 2 diabetes	Hepatic steatosis
Raloxifene	Osteoporosis	Breast cancer
Tamoxifen	Breast cancer	Bipolar disorder

Double duty. NIH researchers have found new uses for several therapeutics.

Paving the Way for Prevention, Recovery, and Cure

www.nimh.nih.gov