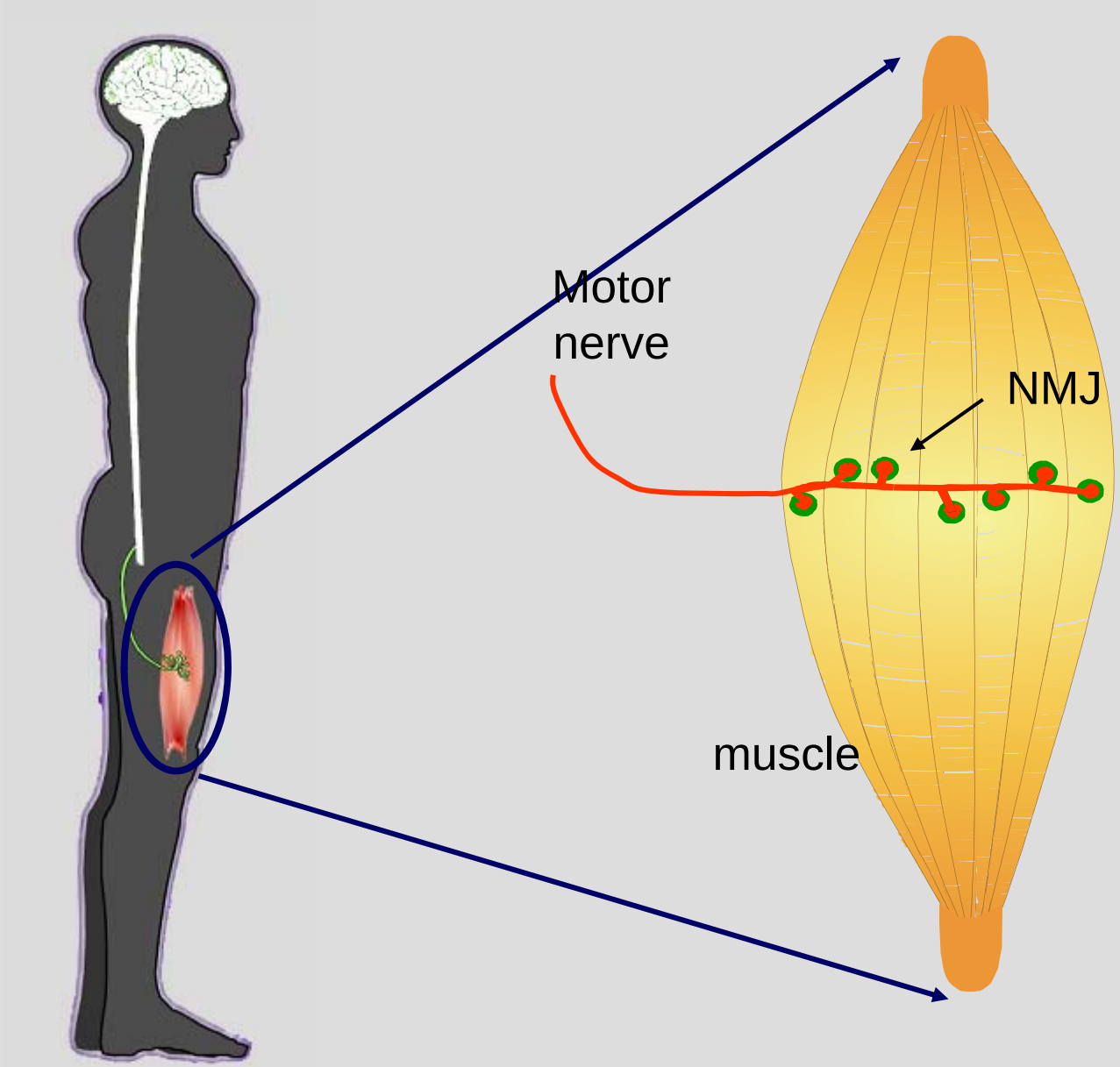
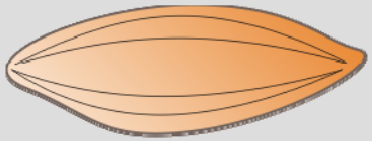
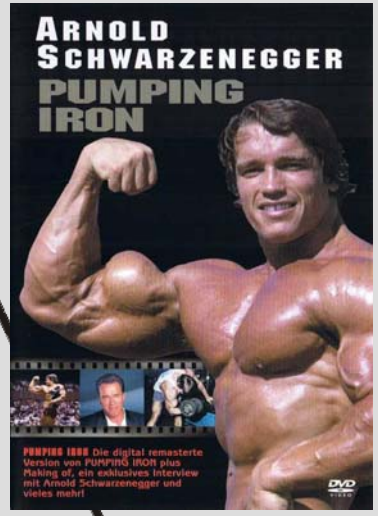
The neuromuscular junction (NMJ)

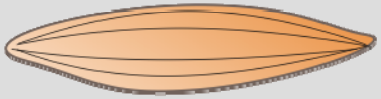


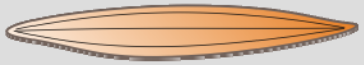
Plasticity of squeletal muscles



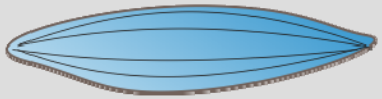
Hypertrophy







Atrophy



Modified fibers

Muscular dystrophies

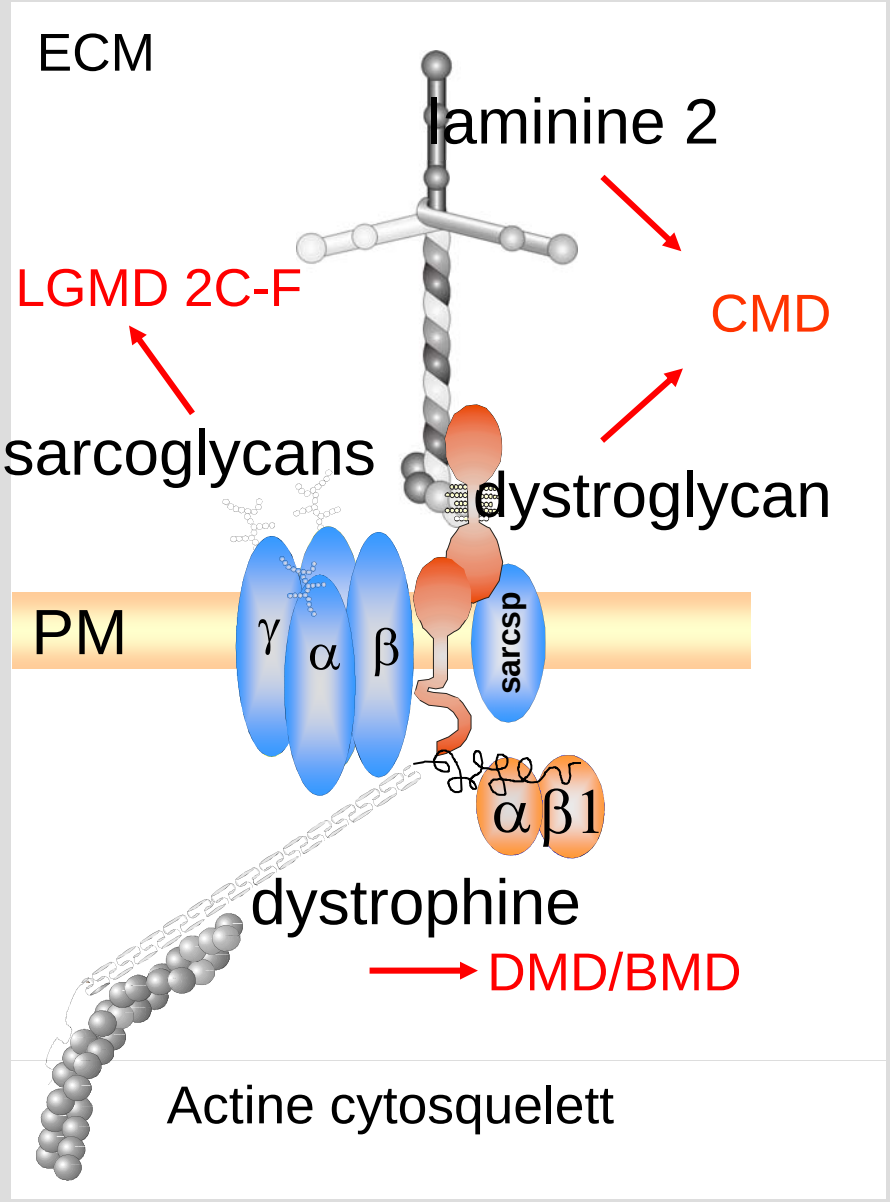
- 1860 First clinical clinical description of a muscular dystrophy
- 1987: Identification of deletions or mutations in the gene of protein dystrophin as causes of the Duchenne and Becker dystrophies

And in 2011?

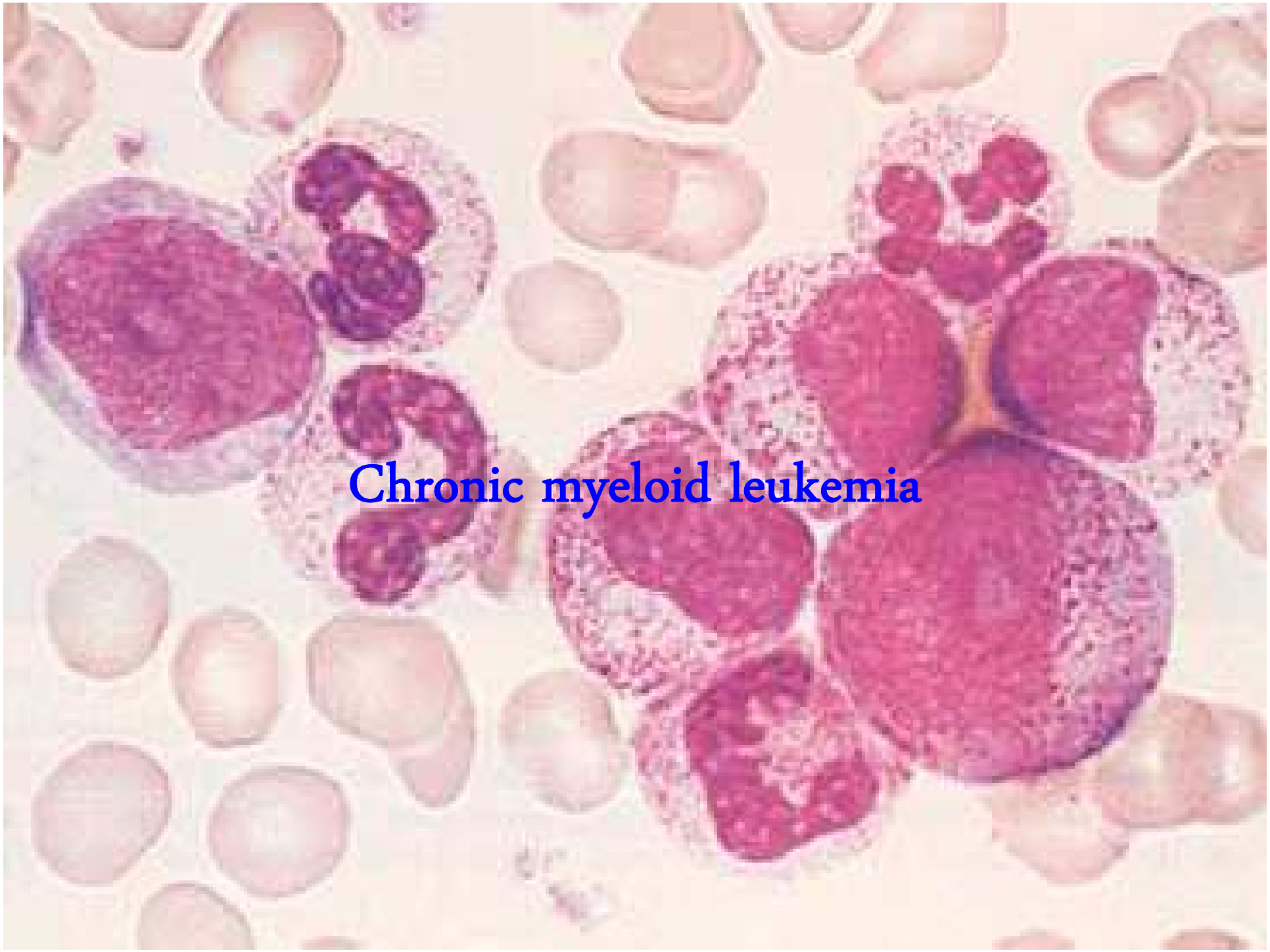
Disorder	Gene locus	Protein defect
Congenital (AR)	6q	Laminin α2 (merosin)
	12q	Laminin receptor (α7 integrin)
	9q	Fukutin (Fukuyama dystrophy)
	1p	Selenoprotein N1 (rigid spine syndrome)
	1p	Glycosyltransferase (muscle-eye-brain disease)
Duchenne and Becker (XR)	Xp21	Dystrophin
Emery-Dreifuss (XR)	Xq28	Emerin
Emery-Dreifuss (AD/AR)	1q	Lamin A/C
Distal (AD)	14q, 2q	?
Distal (AR)	2p	Dysferlin
Facioscapulohumeral (AD)	4q	?
Oculopharyngeal (AD)	14q	Poly(A)-binding protein 2 (PAB 2)
Limb-girdle (AD)		
1A	5q	Myotilin
1B	1q	Lamin A/C
1C	3p	Caveolin 3
1D	6q	?
1E	7q	?
1F	2q	?
Limb-girdle (AR)		
2A	15q	Calpain-3
2B	2p	Dysferlin
2C	13q	γ-sarcoglycan
2D	17q	α-sarcoglycan (adhalin)
2E	4q	β-sarcoglycan
2F	5q	δ-sarcoglycan
2G	17q	Telethonin
2H	9q	?
2I	19q	Fukutin-related

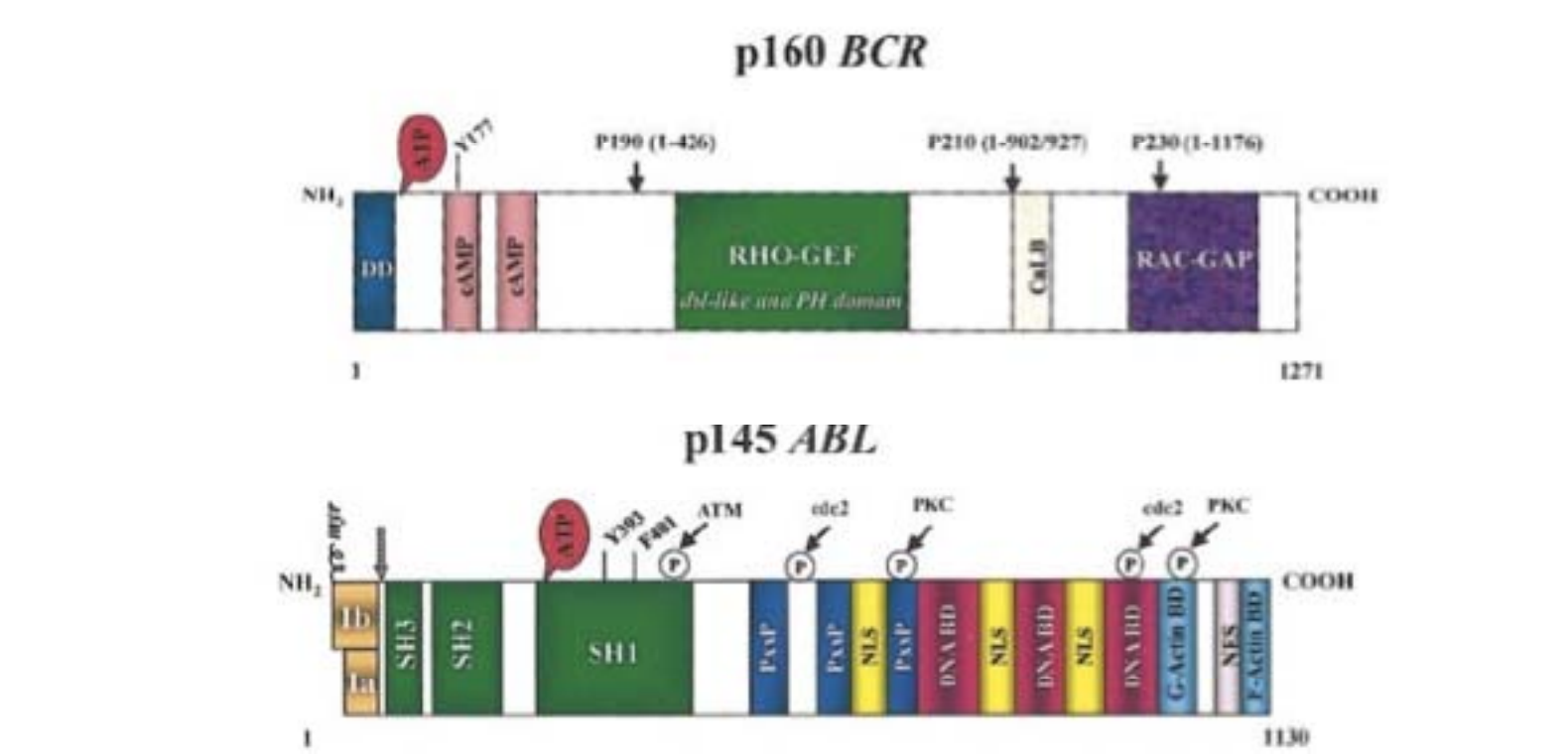
Modes of inheritance: AR=autosomal recessive; AD=autosomal dominant; XR=X-linked recessive. ?=unknown.

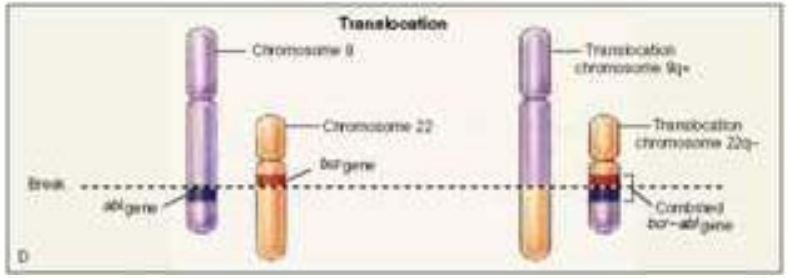
The DGP complex in muscular dystrophies



Therapies ?


Chronic myeloid leukemia





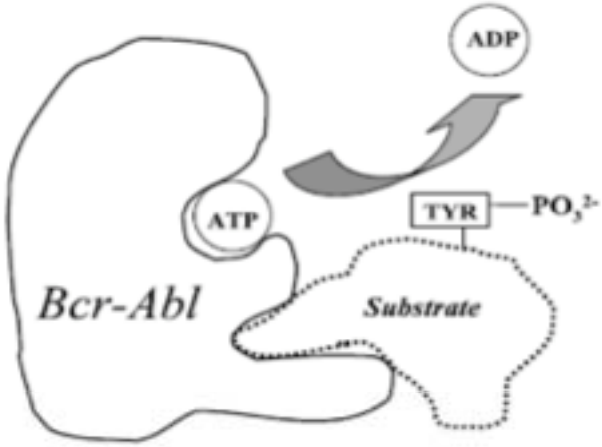
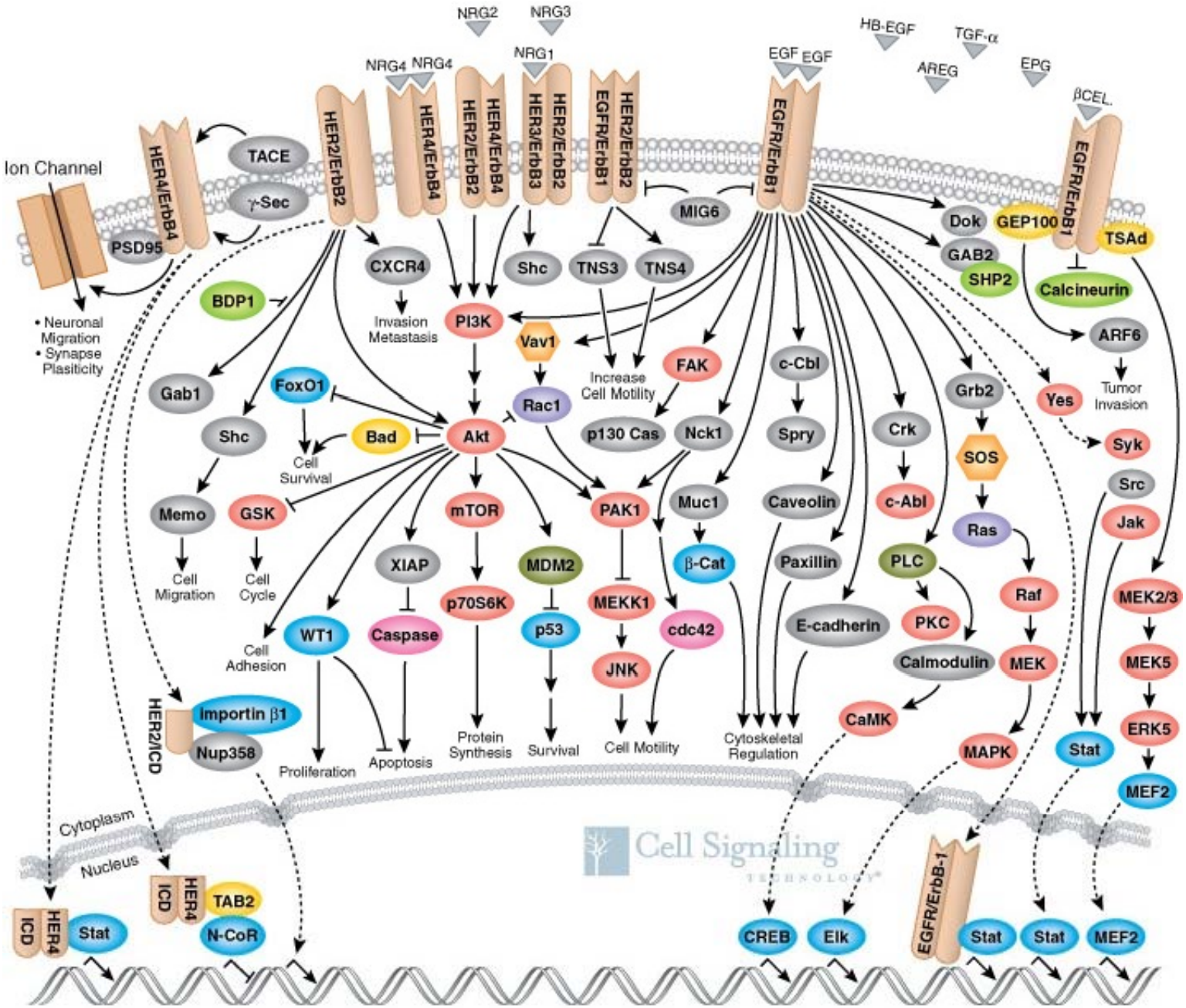


Fig. 1. A simplified representation illustrating the likely mode of act to the kinase activation domain of Bcr-Abl oncoprotein.


NRG2
NRG3
NRG4
NRG4
NRG1
HB-EGF
TGF-α
AREG
EPG
EGF
EGF
βCEL.
Ion Channel
HER4/ErbB4
TACE
γ-Sec
PSD95
HER2/ErbB2
HER4/ErbB4
HER2/ErbB2
HER4/ErbB4
HER3/ErbB3
HER2/ErbB2
EGFR/ErbB1
HER2/ErbB2
EGFR/ErbB1
MIG6
EGFR/ErbB1
Dok
GEP100
GAB2
SHP2
TSAd
Calcineurin
• Neuronal Migration
• Synapse Plasticity
BDP1
CXCR4
Invasion Metastasis
Shc
TNS3
TNS4
PI3K
Vav1
Increase Cell Motility
FAK
c-Cbl
Grb2
Yes
ARF6
Tumor Invasion
Gab1
FoxO1
Rac1
Shc
Bad
Akt
p130 Cas
Nck1
Spry
Crk
SOS
Syk
Cell Survival
Src
Memo
GSK
mTOR
PAK1
Muc1
Caveolin
c-Abl
Ras
Jak
Cell Migration
Cell Cycle
XIAP
MDM2
β-Cat
Paxillin
PLC
Raf
MEK2/3
WT1
Caspase
p70S6K
p53
MEKK1
cdc42
E-cadherin
PKC
MEK
MEK5
Cell Adhesion
JNK
Calmodulin
ERK5
Importin β1
HER2/ICD
Nup358
CaMK
MAPK
Stat
MEF2
Proliferation
Apoptosis
Protein Synthesis
Survival
Cell Motility
Cytoskeletal Regulation
Cytoplasm
Nucleus
Cell Signaling
TECHNOLOGY
ICD
HER4
Stat
ICD
HER4
TAB2
N-CoR
CREB
Elk
EGFR/ErbB-1
Stat
Stat
MEF2

Some definitions in genomic analysis:

CNEs: functional conserved non-coding elements

HCNEs: highly conserved non-coding elements

ncRNAs: functional non-protein-coding RNAs
including miRNAs: micro RNAs

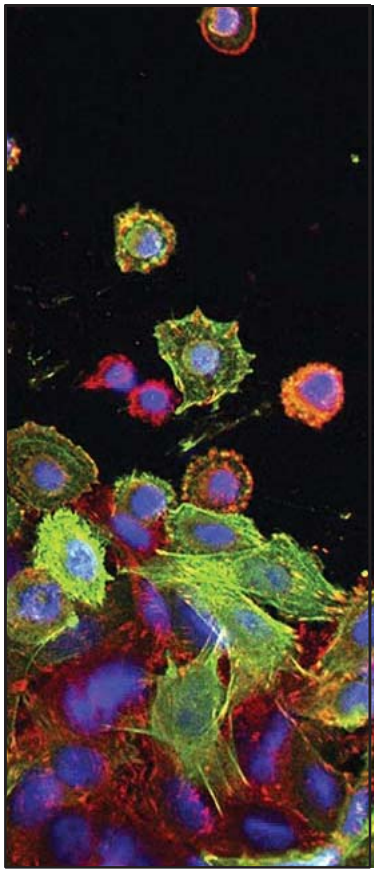
lincRNAs: large intergenic non-coding RNAs

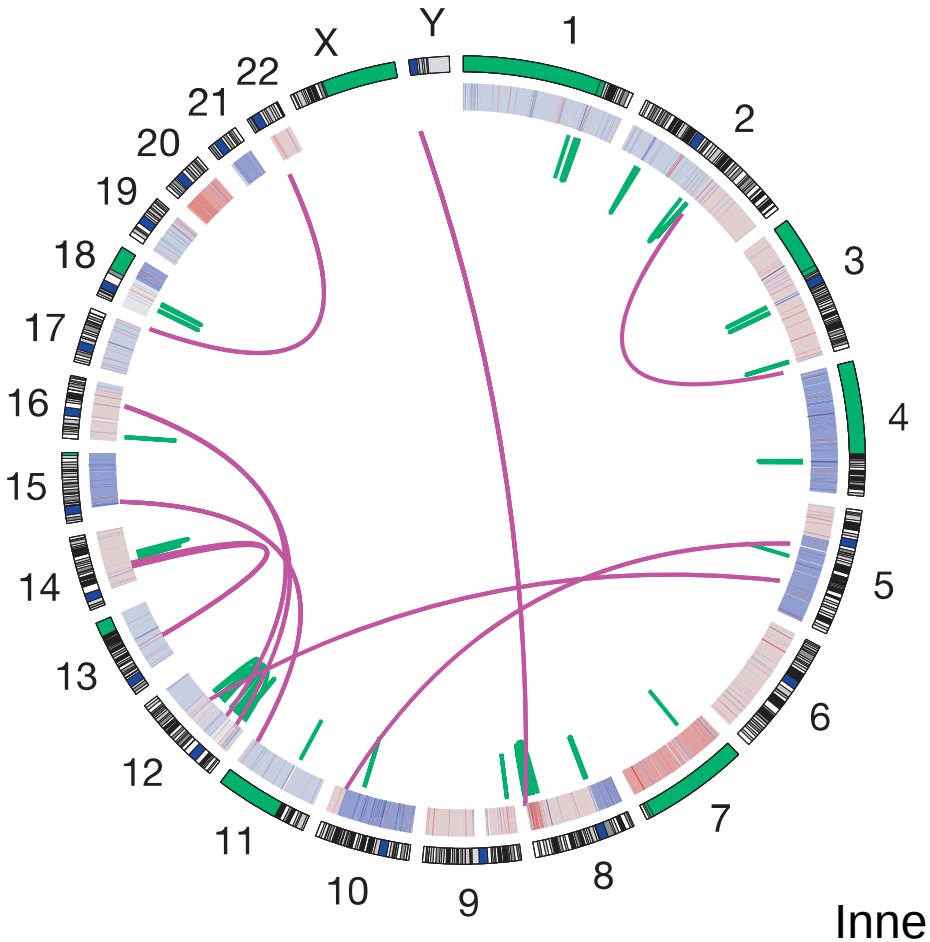
SNPs: single nucleotides polymorphism

CNP (CNV): copy-number polymorphism

GWAS: genome-wide associated study
➔ risk loci

Colon cancer genome maps





Inner ring:

Interchromosomal translocations

Intrachromosomal translocations

Amplifications

Deletions

Genetics of lipids

- GWAS of plasma lipid levels, a major risk factor for myocardial infarction
- Study of 100,000 individuals of European ancestry: identification of 95 loci associated to low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides.
- nearly all of the 18 genes previously implicated in rare Mendelian lipid disorders included
- HMGCR locus has a common variant at 40% frequency that changes LDL by a modest 2.8 mg/dl and no known rare mutations of large effect, presumably because they would be lethal.

- **New loci identified:**

- sortilin gene (SORT1): a novel transcription-factor-binding site that leads to altered plasma LDL levels

- a pair of common nonsense variants in the PCSK9 gene in African-Americans (2.6% combined frequency) that markedly reduces both LDL levels and risk of myocardial infarction

- null allele are healthy indicating that a drug against the encoded protein should be safe and effective

Neurodegenerative diseases

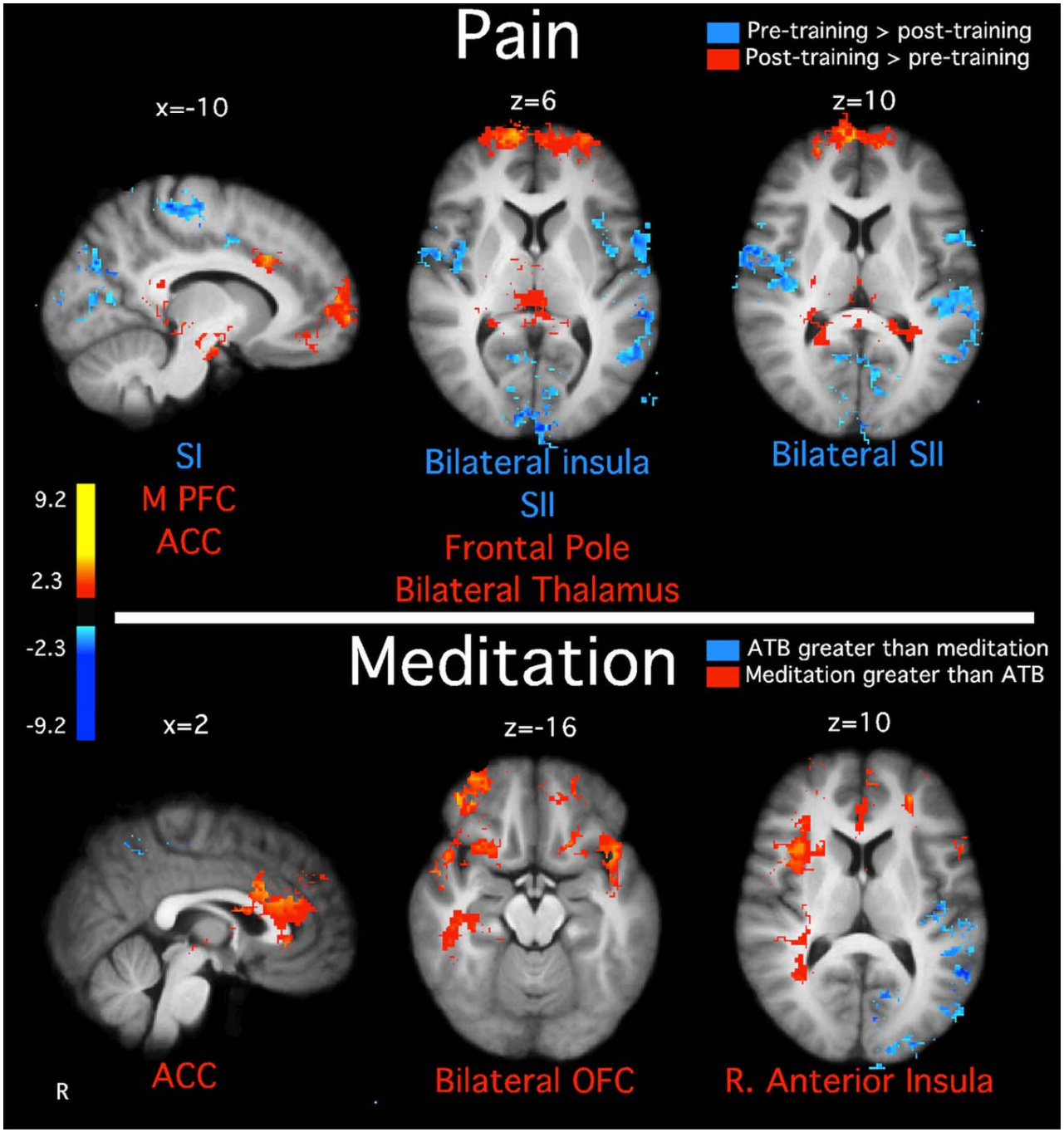
Parkinson disease: mostly sporadic:
LRRK2, *PARK2*, *PARK7*, *PINK1*, *SNCA GBA*, *SNCAIP*, or *UCHL1* as candidate genes

Alzheimer's disease sporadic form:
APOE e2, APOE e3, APOE e4 (genetic linkeage)

GWAS identified:
SORL1, CLU, CR1, PICALM

Alzheimer's disease early onset*:*

APP, *PSEN1*, or *PSEN2*


Pain
Pre-training > post-training
Post-training > pre-training
x=-10
z=6
z=10
SI
M PFC
ACC
Bilateral insula
SII
Frontal Pole
Bilateral Thalamus
Bilateral SII
9.2
2.3
-2.3
-9.2
Meditation
ATB greater than meditation
Meditation greater than ATB
x=2
z=-16
z=10
ACC
Bilateral OFC
R. Anterior Insula
R

Issues of the Conference:

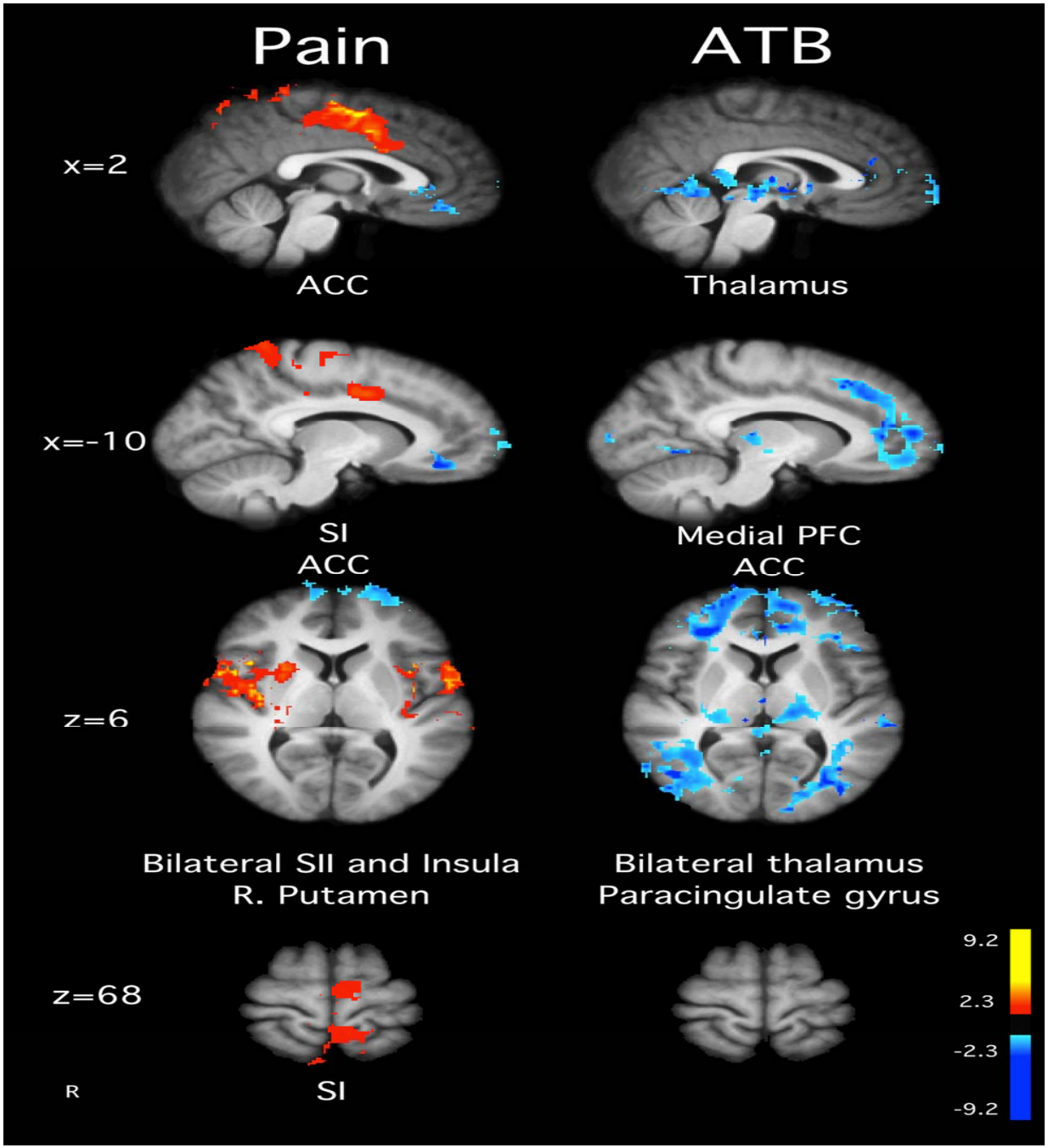
- Future of personalized medicine?
    a) Diagnostic
    b) Treatment

- Legal consequences?
    a) Insurances
    b) Professional life

- Acceptance by the society?

- Consequences for the society?
    a) Personal decisions
    b) Social and community decisions

Others?


Pain
ATB
x=2
ACC
Thalamus
x=-10
SI
ACC
Medial PFC
ACC
z=6
Bilateral SII and Insula
R. Putamen
Bilateral thalamus
Paracingulate gyrus
z=68
SI
R
9.2
2.3
-2.3
-9.2