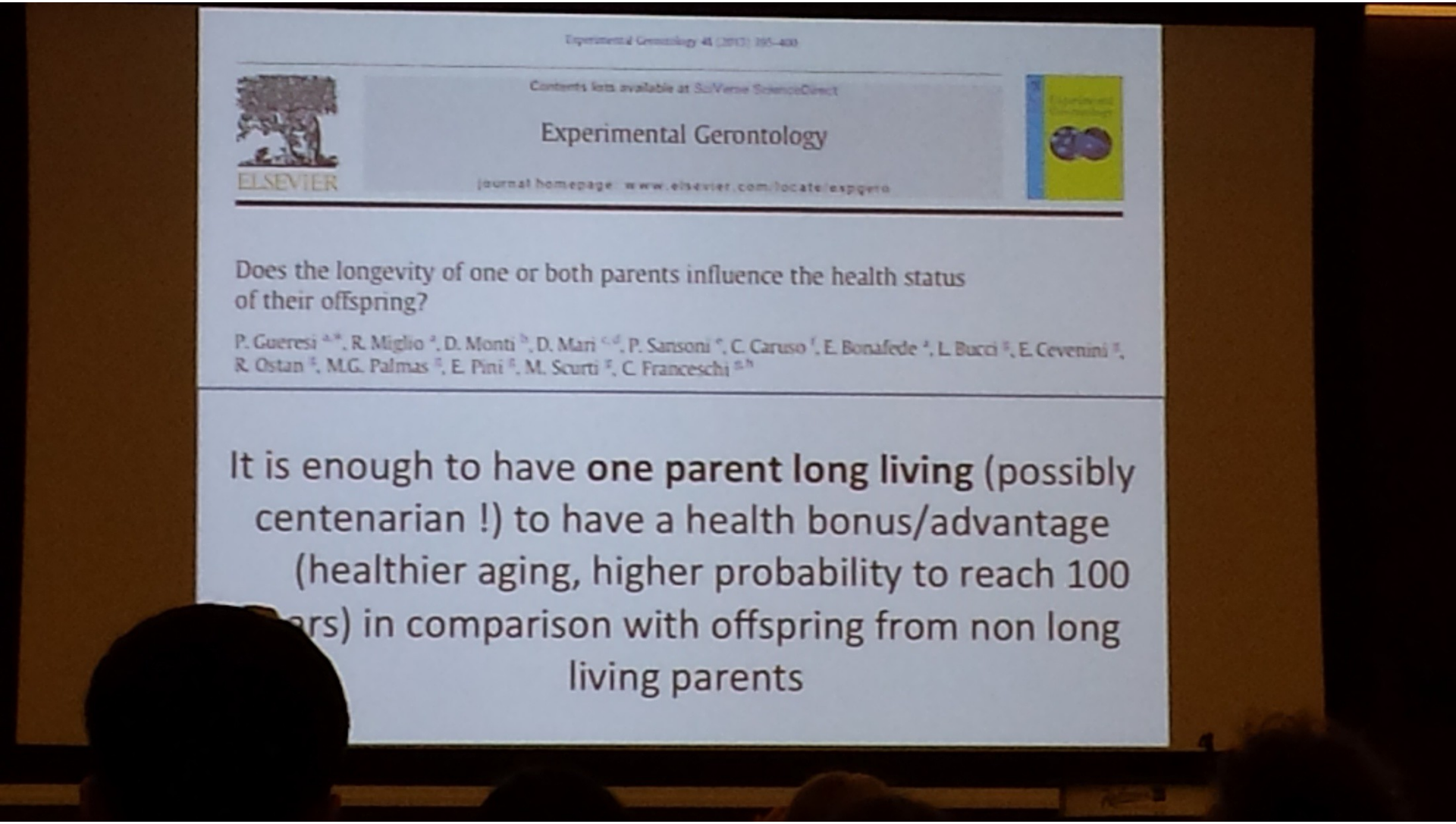
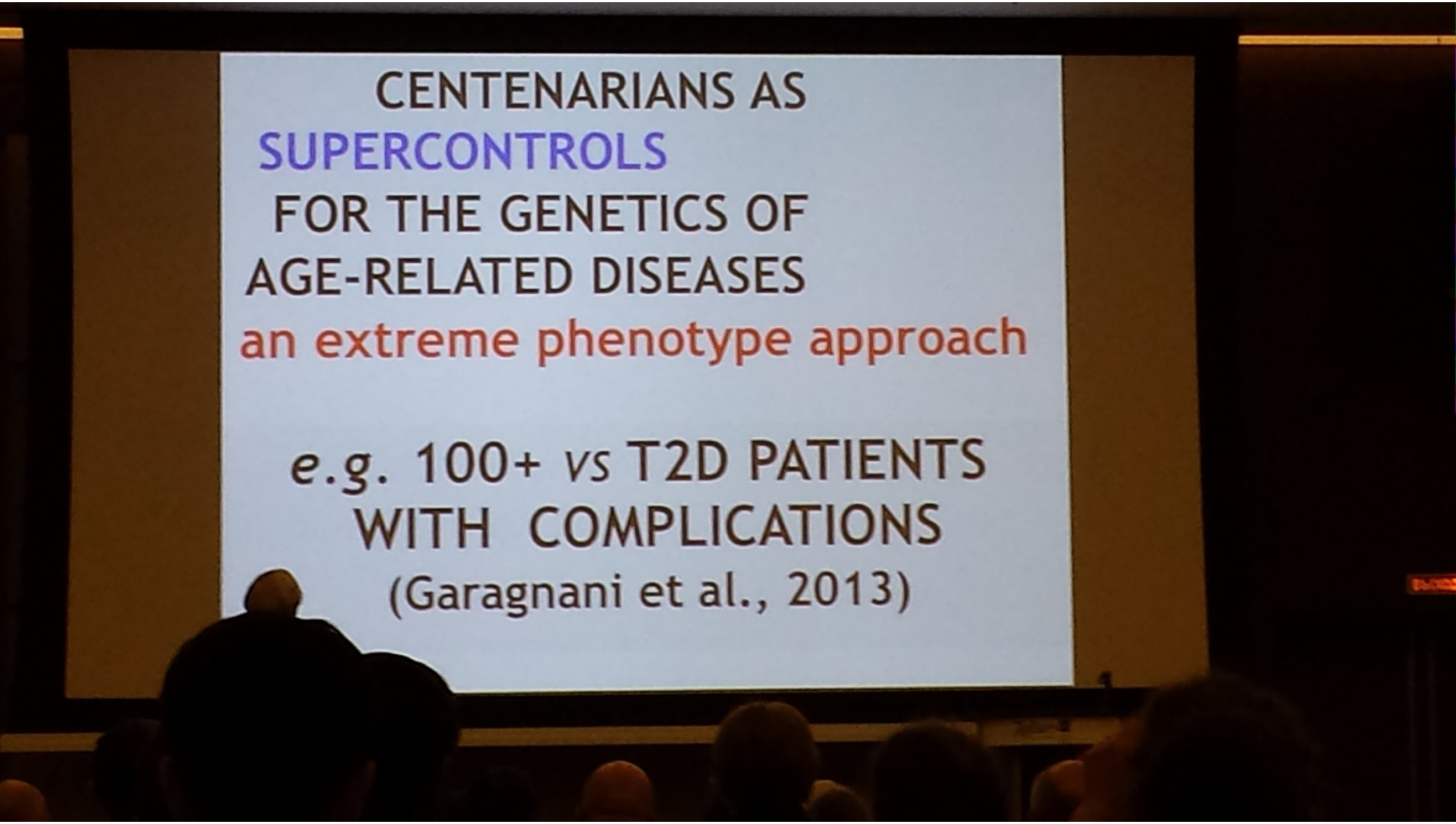
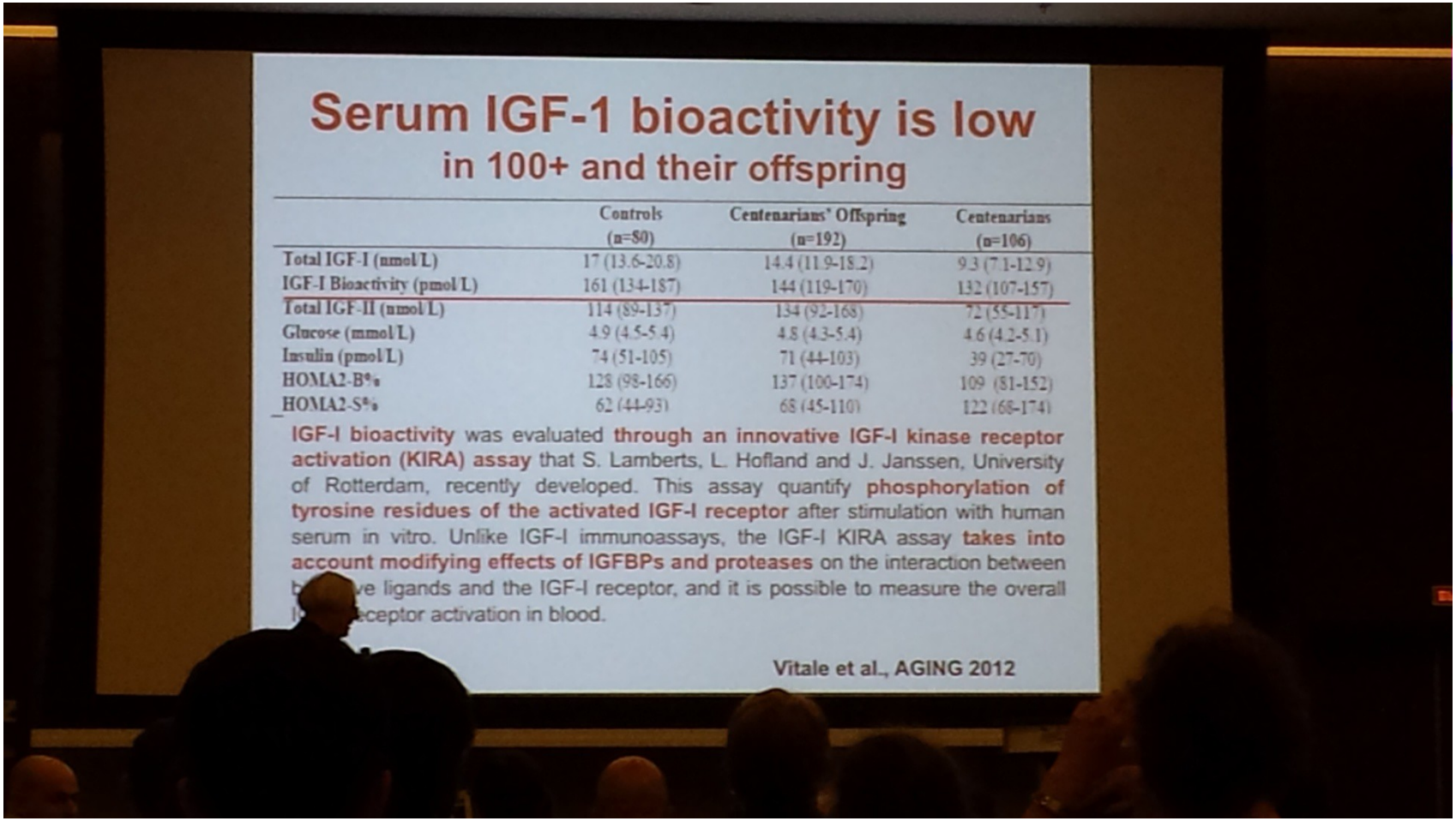
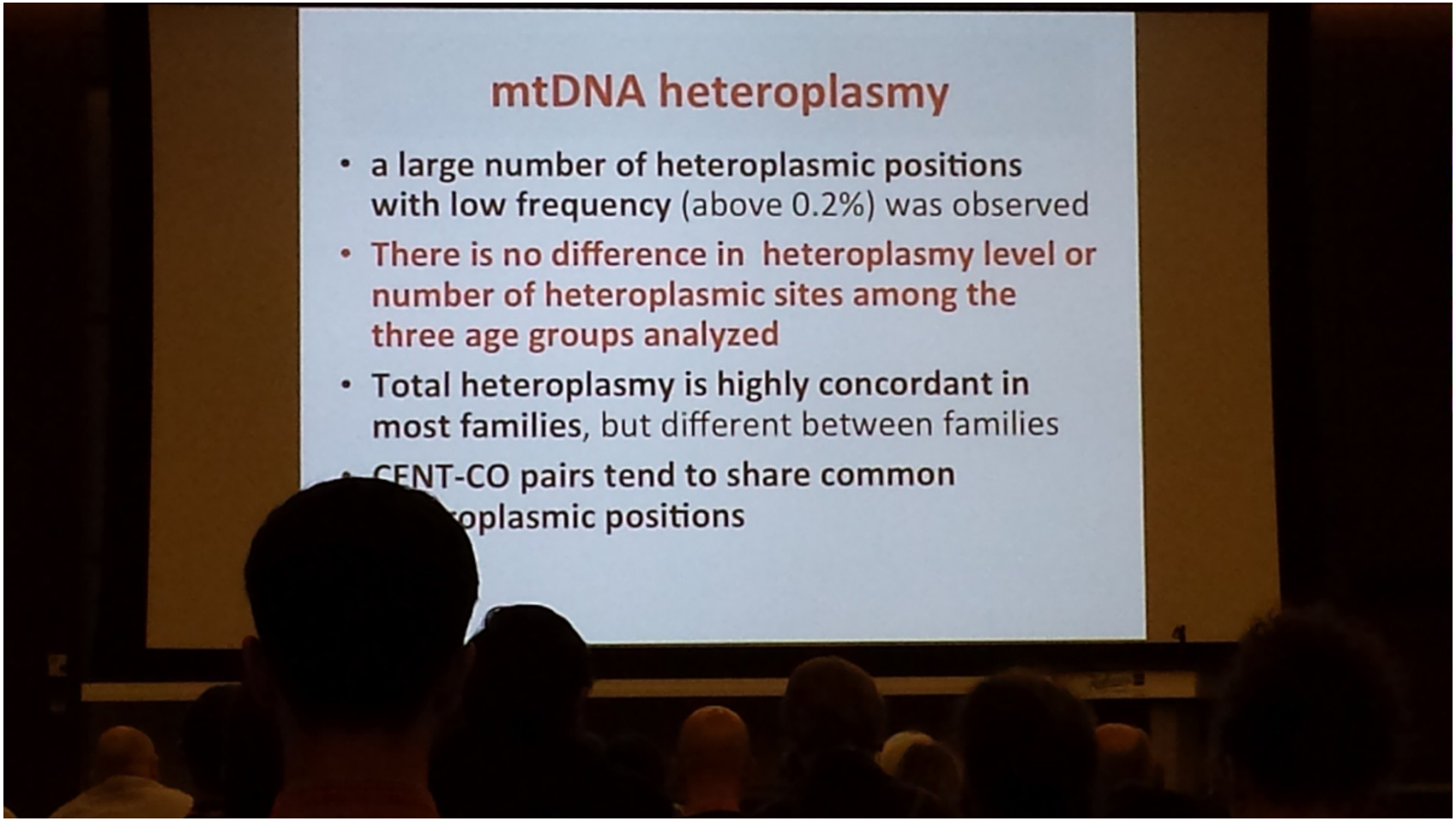
6–10 апреля 2014 года в Сочи III Международную Конференцию «Генетика старения и долголетия»

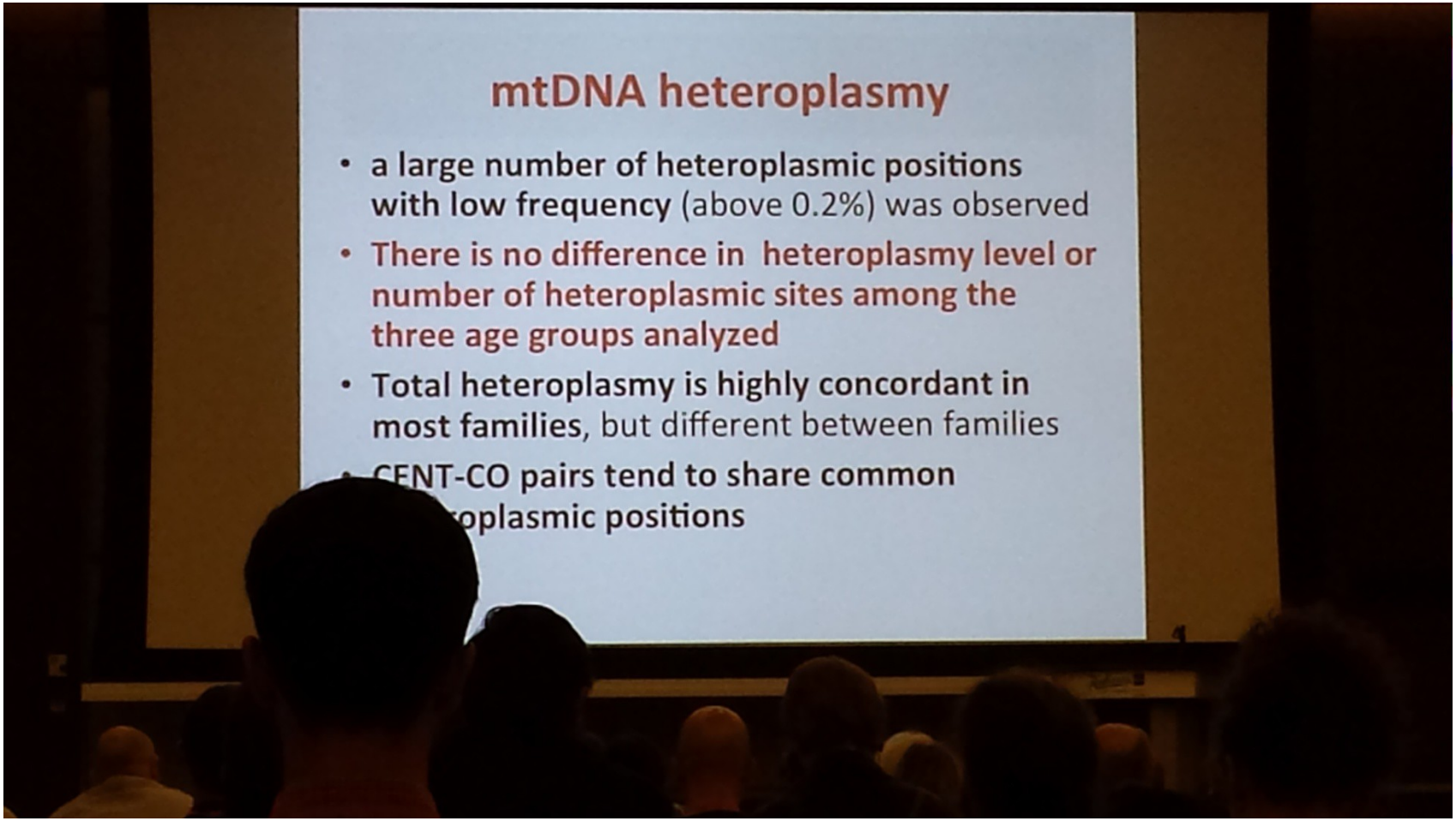
Мы




CENTENARIANS AS
SUPERCONTROLS
FOR THE GENETICS OF
AGE-RELATED DISEASES
an extreme phenotype approach
e.g. 100+ vs T2D PATIENTS
WITH COMPLICATIONS
(Garagnani et al., 2013)


Serum IGF-1 bioactivity is low
in 100+ and their offspring
Controls (n=80)
Centenarians' Offspring (n=192)
Centenarians (n=106)
Total IGF-I (nmol/L) 17 (13.6-20.8) 14.4 (11.9-18.2) 9.3 (7.1-12.9)
IGF-I Bioactivity (pmol/L) 161 (134-187) 144 (119-170) 132 (107-157)
Total IGF-II (nmol/L) 114 (89-137) 134 (92-168) 72 (55-117)
Glucose (mmol/L) 4.9 (4.5-5.4) 4.8 (4.3-5.4) 4.6 (4.2-5.1)
Insulin (pmol/L) 74 (51-105) 71 (44-103) 39 (27-70)
HOMA2-B% 128 (98-166) 137 (100-174) 109 (81-152)
HOMA2-S% 62 (44-93) 68 (45-110) 122 (68-174)
IGF-I bioactivity was evaluated through an innovative IGF-I kinase receptor activation (KIRA) assay that S. Lamberts, L. Hofland and J. Janssen, University of Rotterdam, recently developed. This assay quantify phosphorylation of tyrosine residues of the activated IGF-I receptor after stimulation with human serum in vitro. Unlike IGF-I immunoassays, the IGF-I KIRA assay takes into account modifying effects of IGFBPs and proteases on the interaction between
ligands and the IGF-I receptor, and it is possible to measure the overall
eptor activation in blood.
Vitale et al., AGING 2012


mtDNA heteroplasmy
• a large number of heteroplasmic positions with low frequency (above 0.2%) was observed
• There is no difference in heteroplasmy level or number of heteroplasmic sites among the three age groups analyzed
• Total heteroplasmy is highly concordant in most families, but different between families
• CENT-CO pairs tend to share common
oplasmic positions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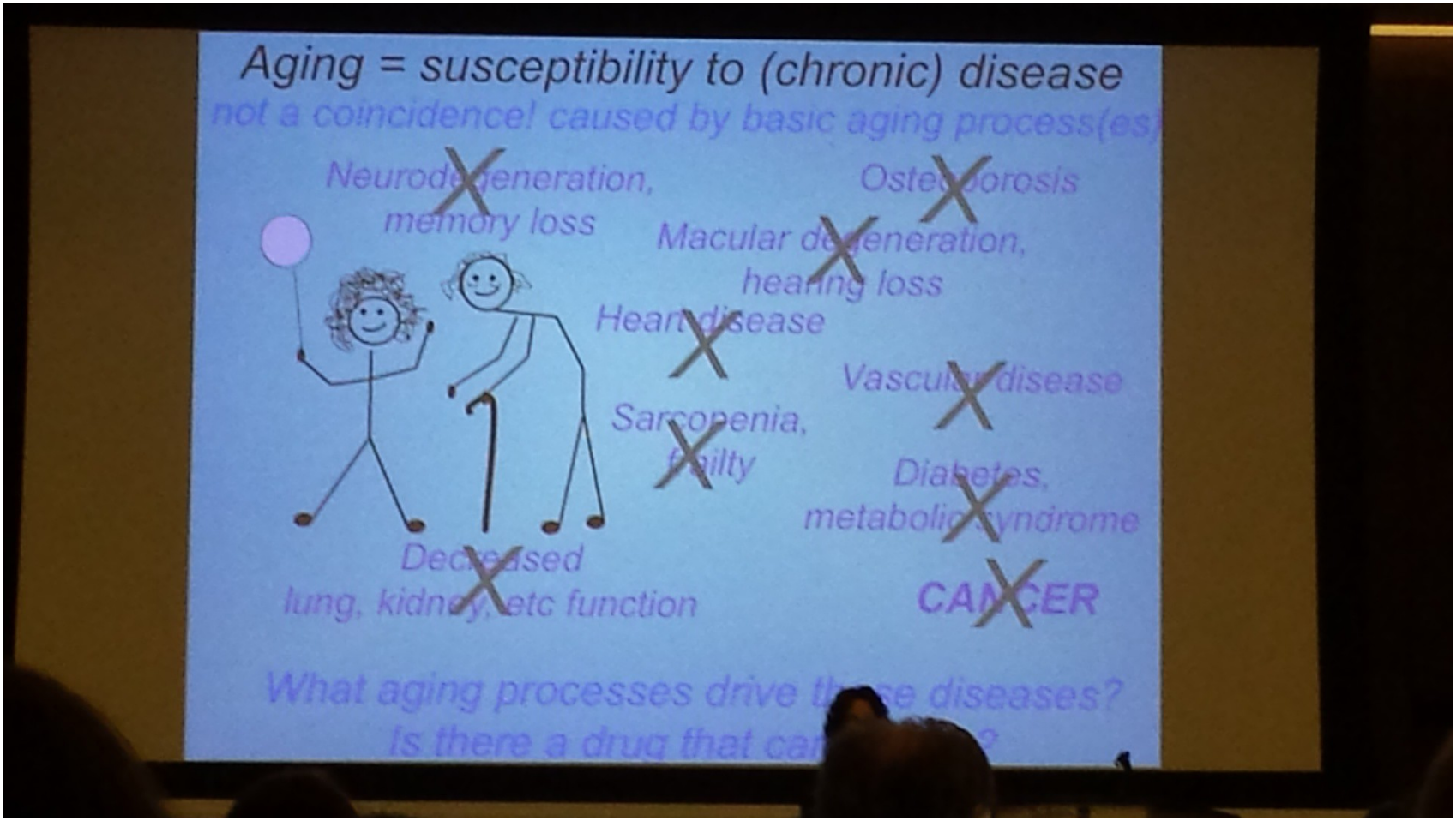
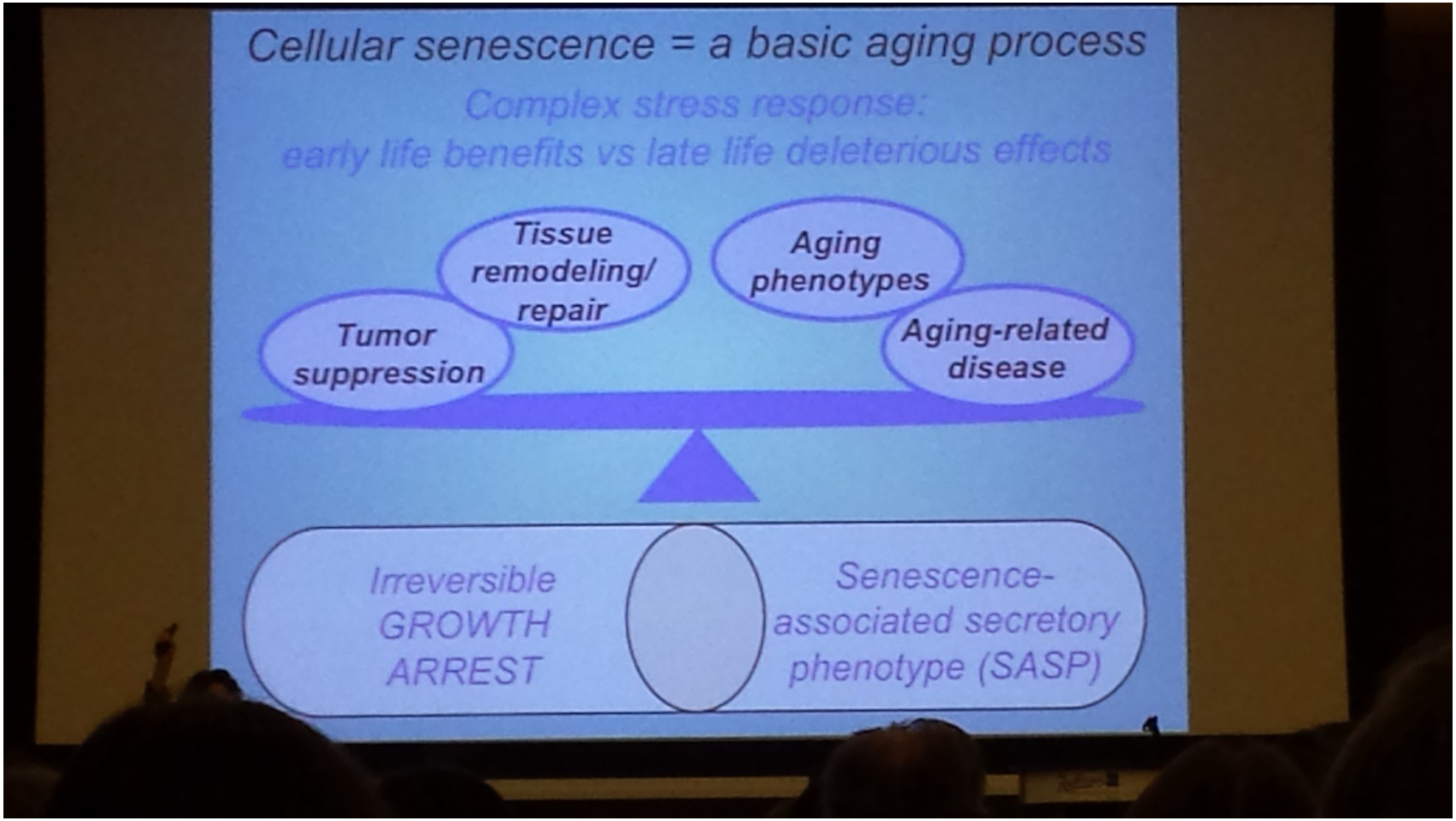
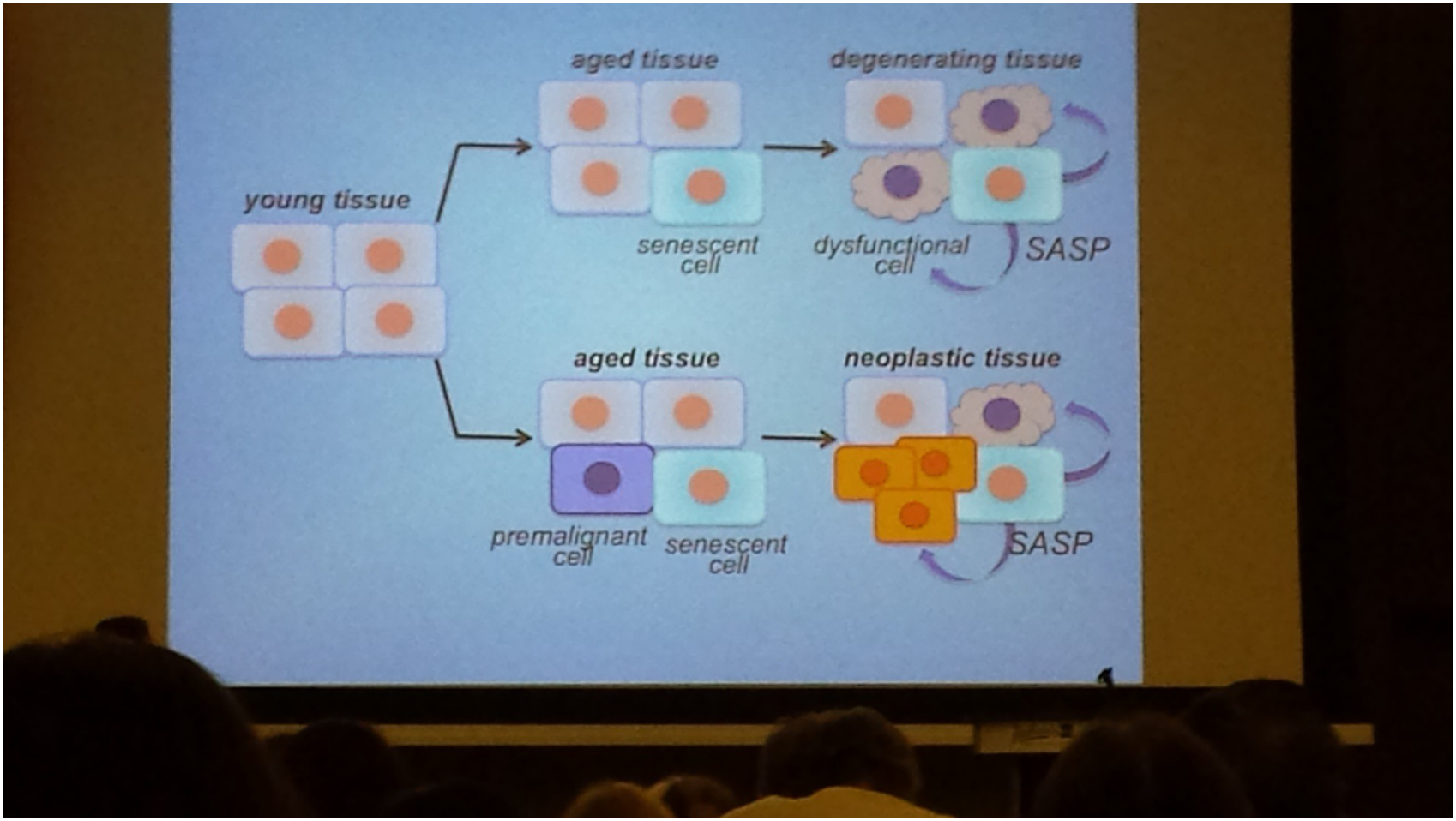

Aging = susceptibility to (chronic) disease
not a coincidence! caused by basic aging process(es)
Neurodegeneration, memory loss
Osteoporosis
Macular degeneration, hearing loss
Heart disease
Vascular disease
Sarcopenia, frailty
Diabetes, metabolic syndrome
Decreased lung, kidney, etc function
CANCER
What aging processes drive these diseases?
Is there a drug that can


Cellular senescence = a basic aging process
Complex stress response:
early life benefits vs late life deleterious effects
Tissue remodeling/ repair
Aging phenotypes
Tumor suppression
Aging-related disease
Irreversible GROWTH ARREST
Senescence-associated secretory phenotype (SASP)

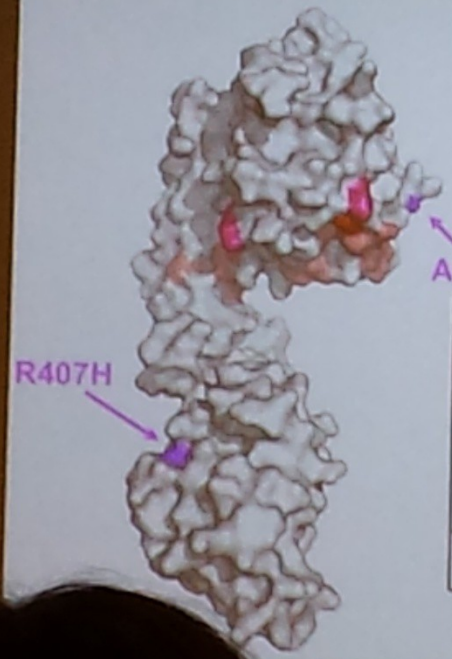

aged tissue
degenerating tissue
young tissue
senescent cell
dysfunctional cell
SASP
aged tissue
neoplastic tissue
premalignant cell
senescent cell
SASP

Breakthrough in Aging Research

Discovery of "conserved" aging genes

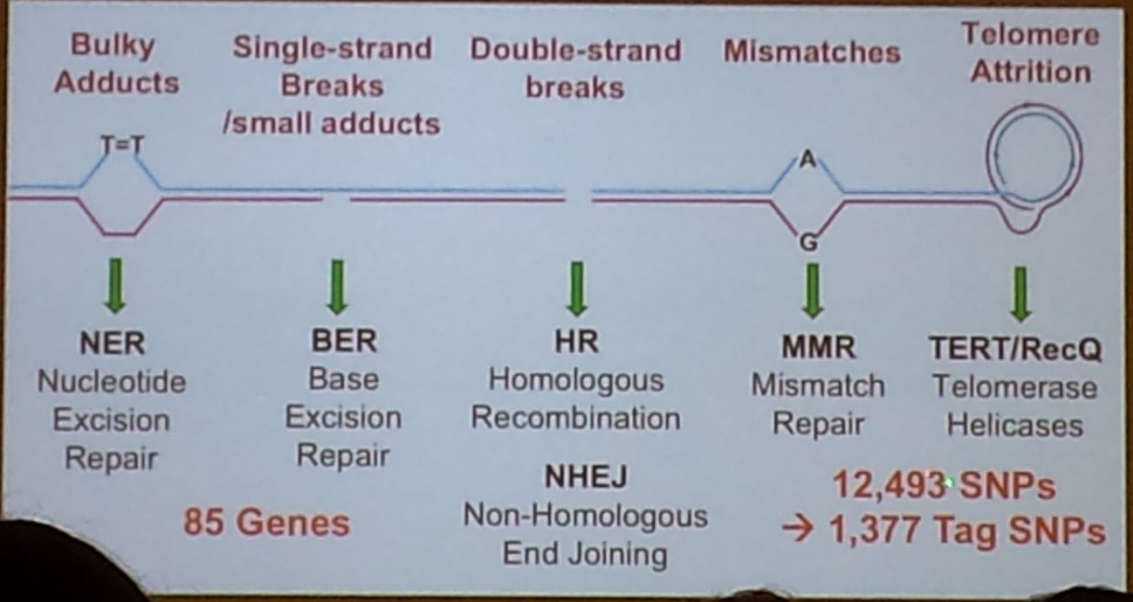
Impact on *Human* Aging?

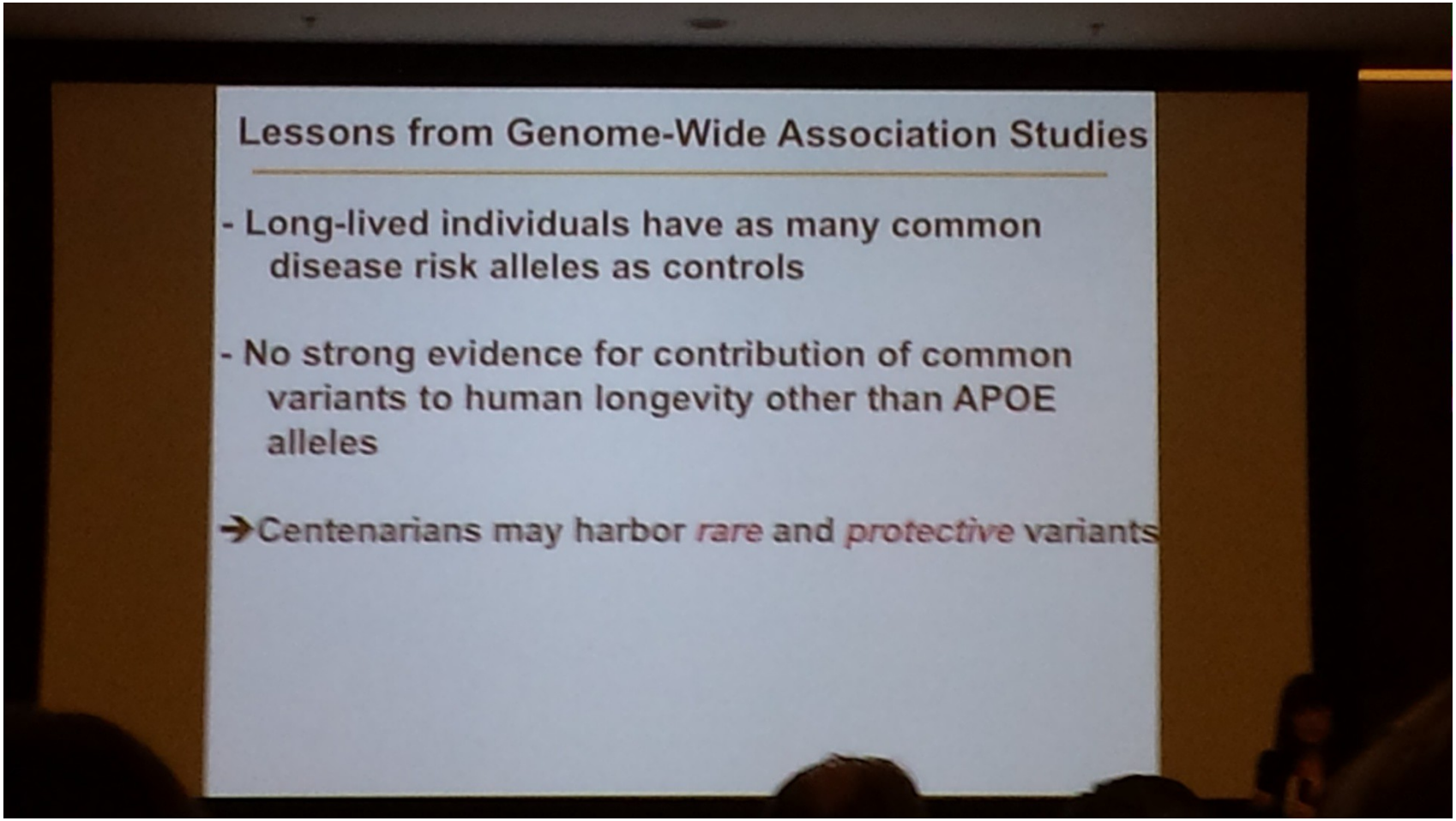
Novel IGF1R missense variants are enriched in centenarians compared to controls

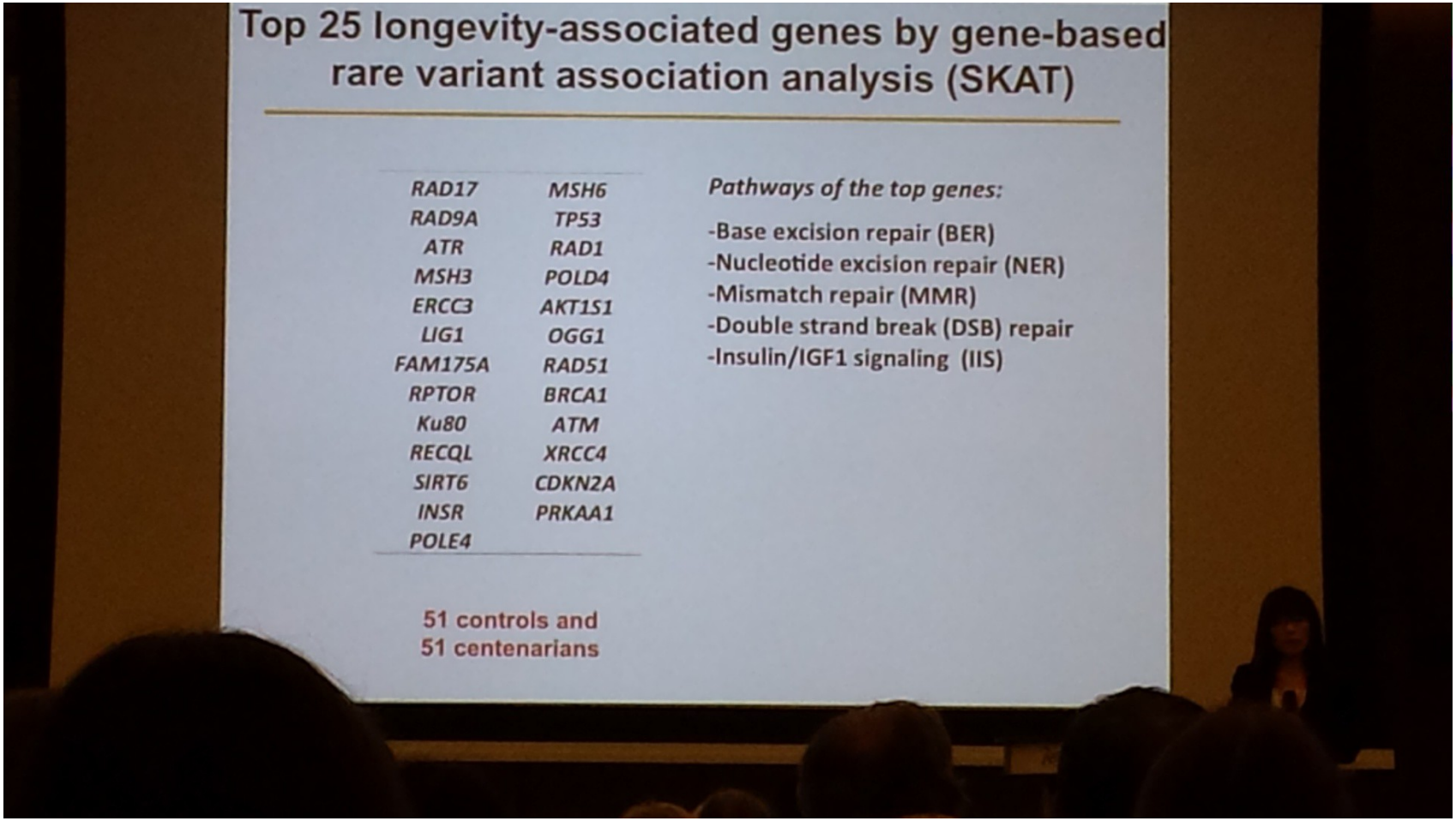


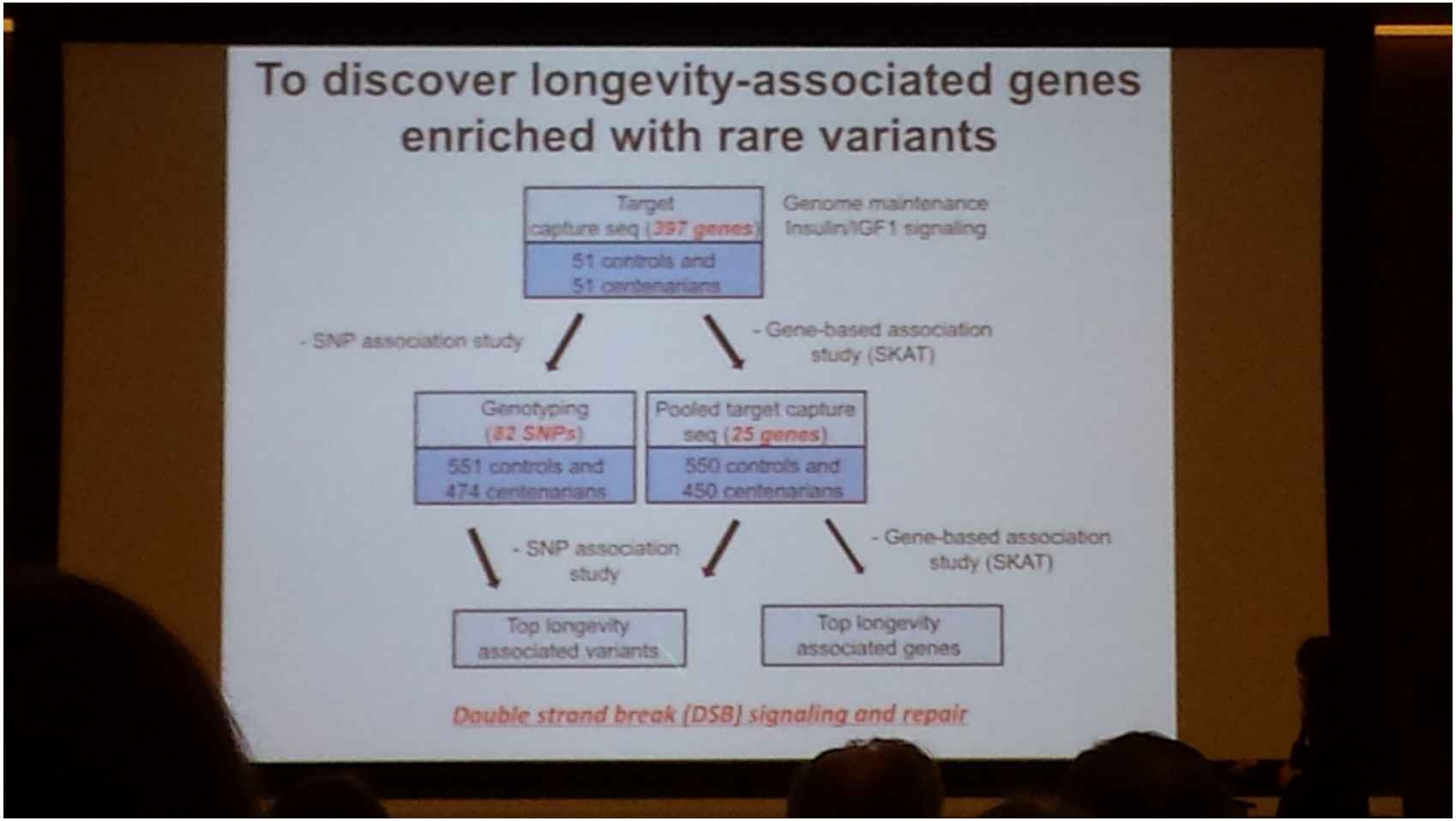
Nature of variation	Centenarians (n=384)	Controls (n=312)
Ala 37 Thr	2	0
Arg 407 His	7	1
significance	*p=0.02*	

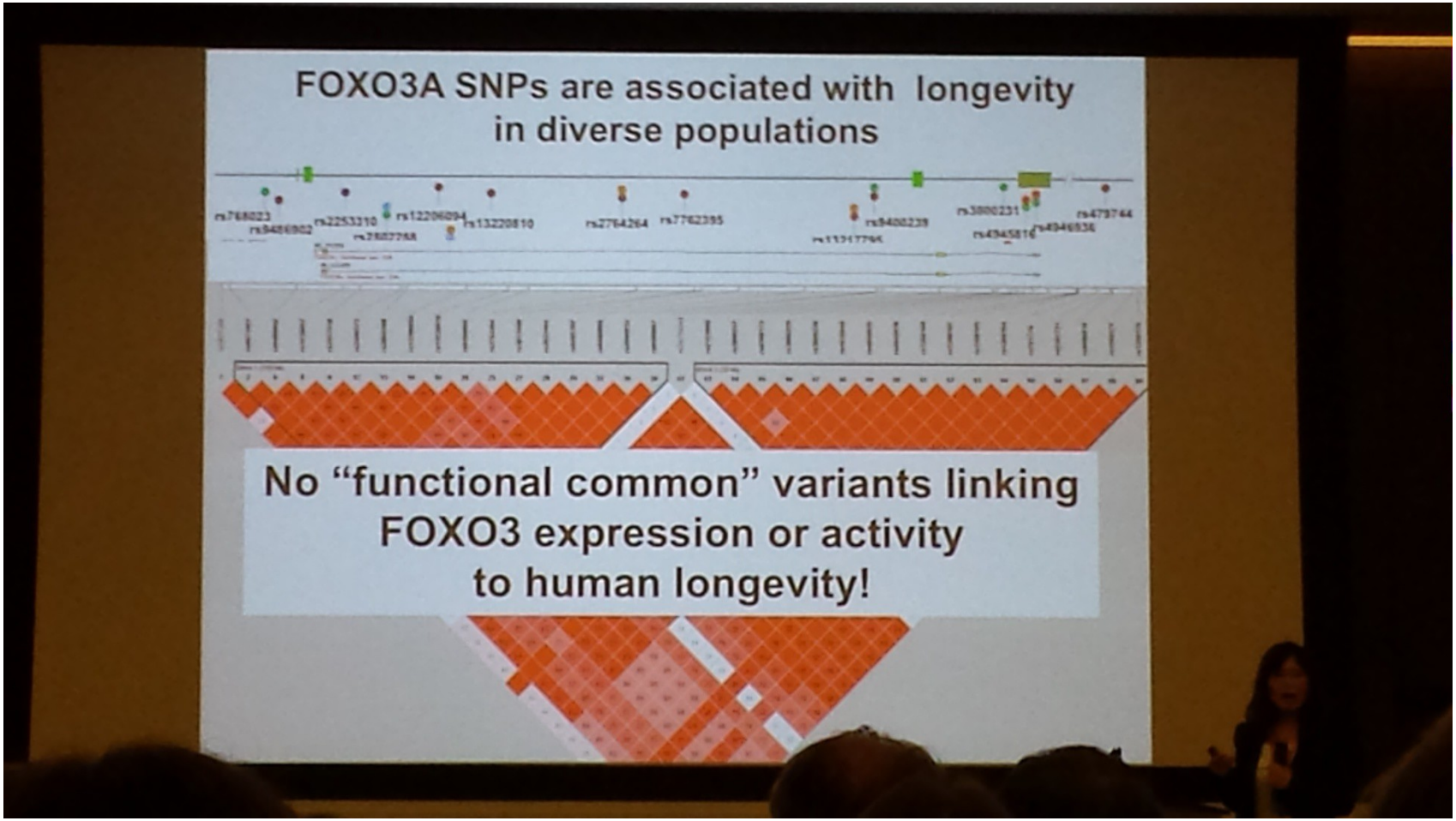
Genome maintenance: Candidate pathways in human aging



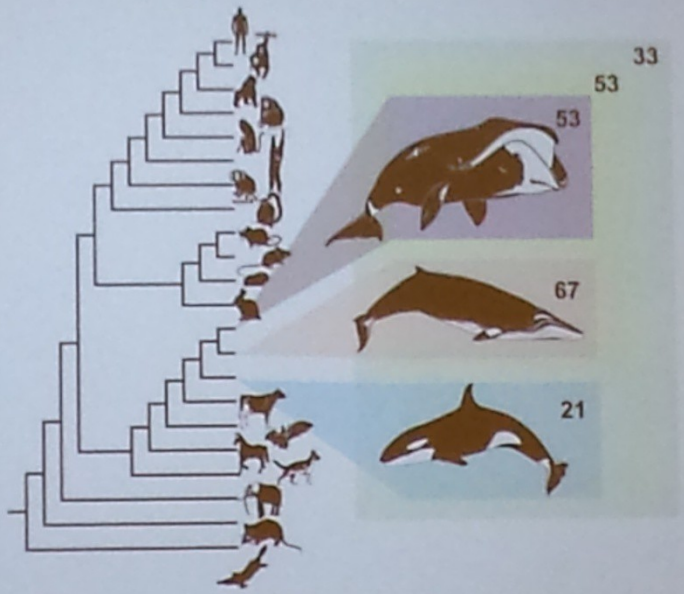

Lessons from Genome-Wide Association Studies
- Long-lived individuals have as many common disease risk alleles as controls
- No strong evidence for contribution of common variants to human longevity other than APOE alleles
→Centenarians may harbor rare and protective variants

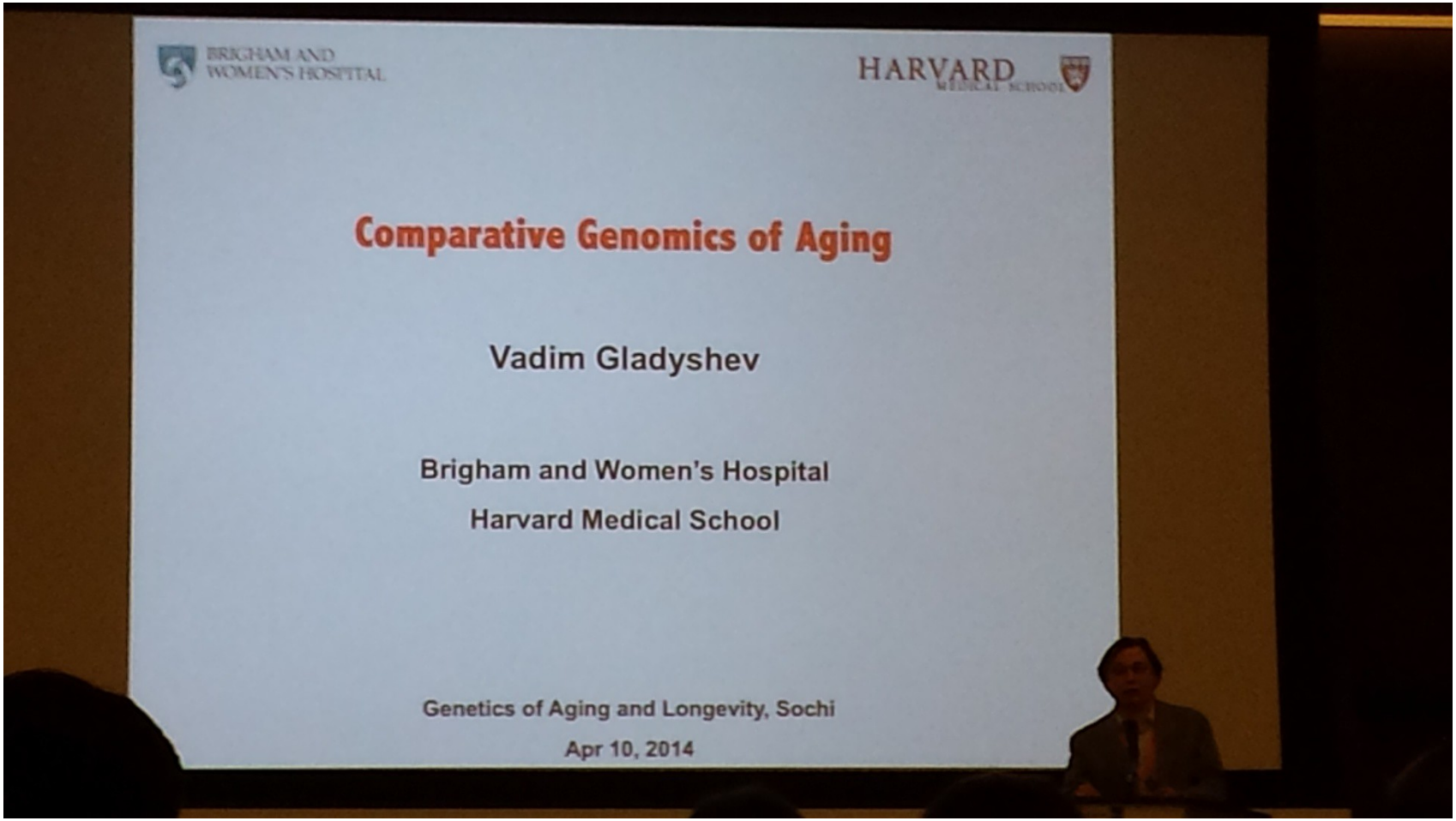

Top 25 longevity-associated genes by gene-based rare variant association analysis (SKAT)
RAD17
RAD9A
ATR
MSH3
ERCC3
LIG1
FAM175A
RPTOR
Ku80
RECQL
SIRT6
INSR
POLE4
MSH6
TP53
RAD1
POLD4
AKT1S1
OGG1
RAD51
BRCA1
ATM
XRCC4
CDKN2A
PRKAA1
Pathways of the top genes:
-Base excision repair (BER)
-Nucleotide excision repair (NER)
-Mismatch repair (MMR)
-Double strand break (DSB) repair
-Insulin/IGF1 signaling (IIS)
51 controls and
51 centenarians

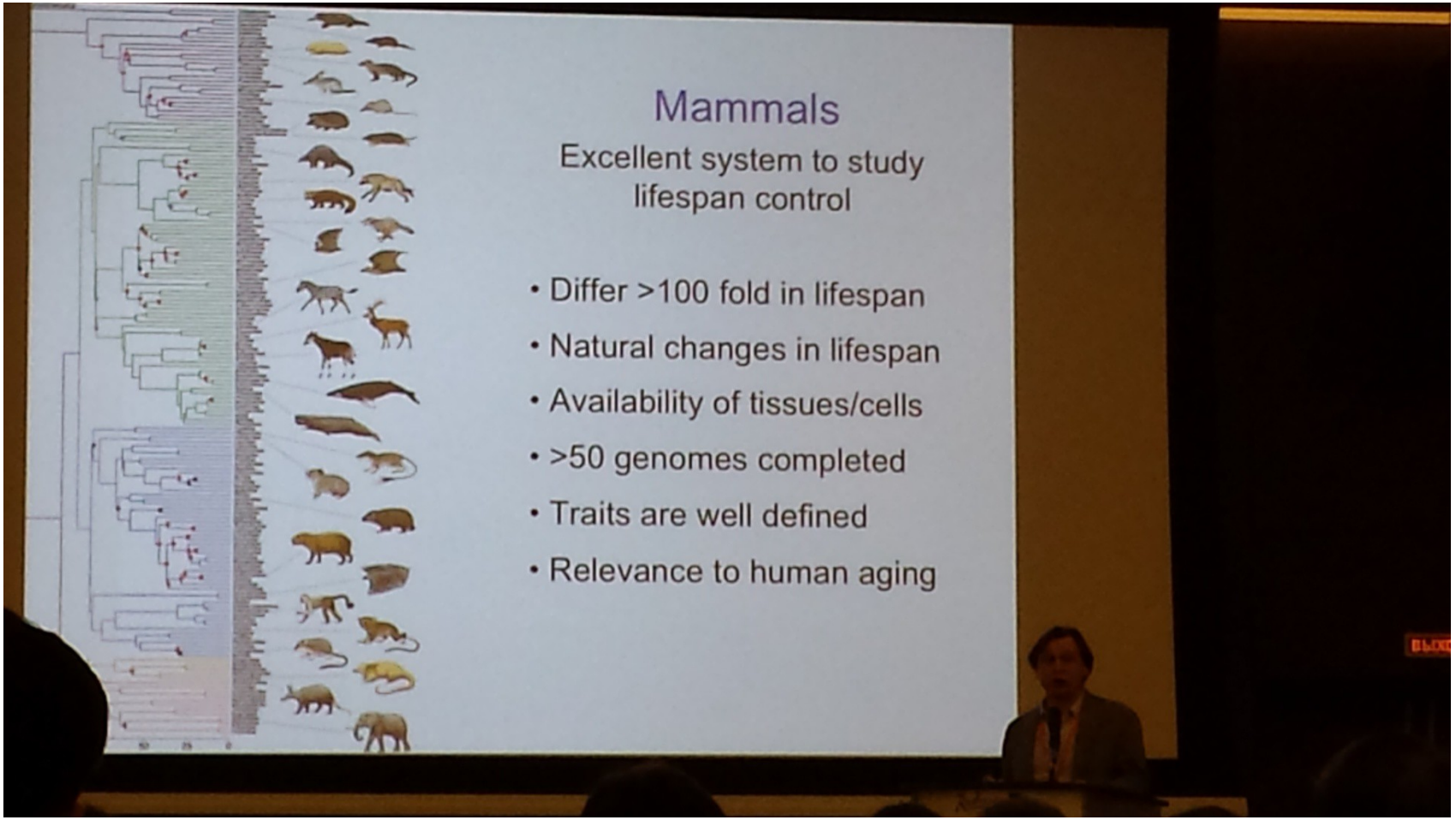

To discover longevity-associated genes enriched with rare variants
Target capture seq (397 genes)
51 controls and 51 centenarians
Genome maintenance
Insulin/IGF1 signaling
- SNP association study
- Gene-based association study (SKAT)
Genotyping (82 SNPs)
551 controls and 474 centenarians
Pooled target capture seq (25 genes)
550 controls and 450 centenarians
- SNP association study
- Gene-based association study (SKAT)
Top longevity associated variants
Top longevity associated genes
Double strand break (DSB) signaling and repair


FOXO3A SNPs are associated with longevity
in diverse populations
rs768023
rs9486902
rs2253310
rs2802268
rs12206094
rs13220810
rs2764264
rs7762395
rs9400239
rs3800231
rs4946816
rs4946936
rs479744
No “functional common” variants linking
FOXO3 expression or activity
to human longevity!

Finding candidate genes in bowhead genome




BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
Comparative Genomics of Aging
Vadim Gladyshev
Brigham and Women's Hospital
Harvard Medical School
Genetics of Aging and Longevity, Sochi
Apr 10, 2014


Mammals
Excellent system to study lifespan control
• Differ >100 fold in lifespan
• Natural changes in lifespan
• Availability of tissues/cells
• >50 genomes completed
• Traits are well defined
• Relevance to human aging

Pairs of related organisms one of which is exceptionally long lived

Naked mole-rat

Damaraland mole-rat

Brandt's bat

Evening bat

Brandt's bat

a

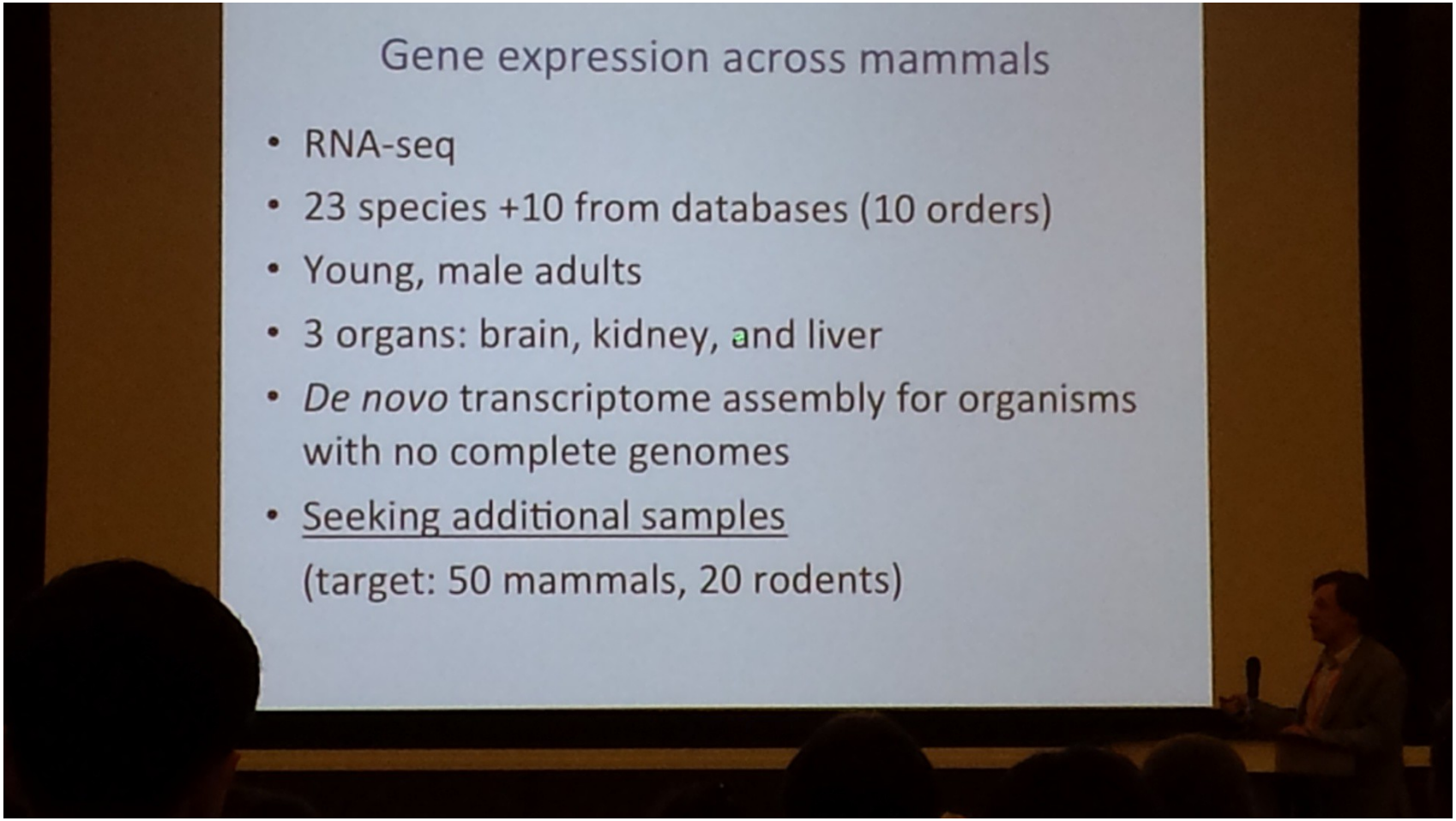
b

Lifespan: >40 years

Body mass: 4-8 g
Hybernation (>6 months)

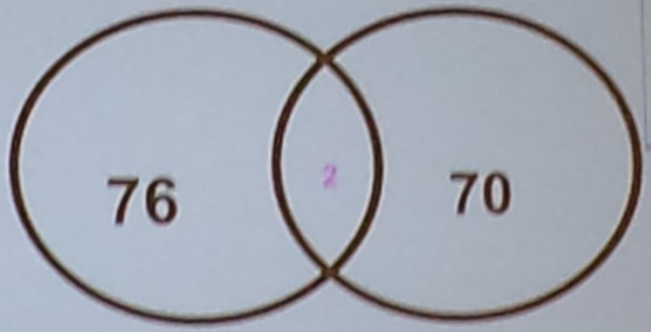
Echolocation
Powered flight

Seim et al (2013) **Genome analysis reveals insights into physiology and longevity of the Brandt's bat *Myotis brandtii*. *Nature Communications*.**


Gene expression across mammals
• RNA-seq
• 23 species +10 from databases (10 orders)
• Young, male adults
• 3 organs: brain, kidney, and liver
• De novo transcriptome assembly for organisms with no complete genomes
• Seeking additional samples
(target: 50 mammals, 20 rodents)

Two widely accepted Breast Carcinoma Prognosis Signatures

Wang et al. Lancet 2005, List = 76 top-ranked genes



Van't Veer, et al. Nature 2002, List = 70 top-ranked genes

	70-gene set	76-gene set	64-gene set	97-gene set	GSR	17-gene set	21-gene set
IBUMAC32	8	2	5	11	2	0	0
70-gene set		2	3	8	1	0	1
76-gene set			1	4	1	0	0
64-gene set				12	3	0	1
97-gene set					8	0	5
GSR						1	1
17-gene set							0

Clinical Cancer Research September 15, 2007 *vol. 13* no. 18 5355-5360