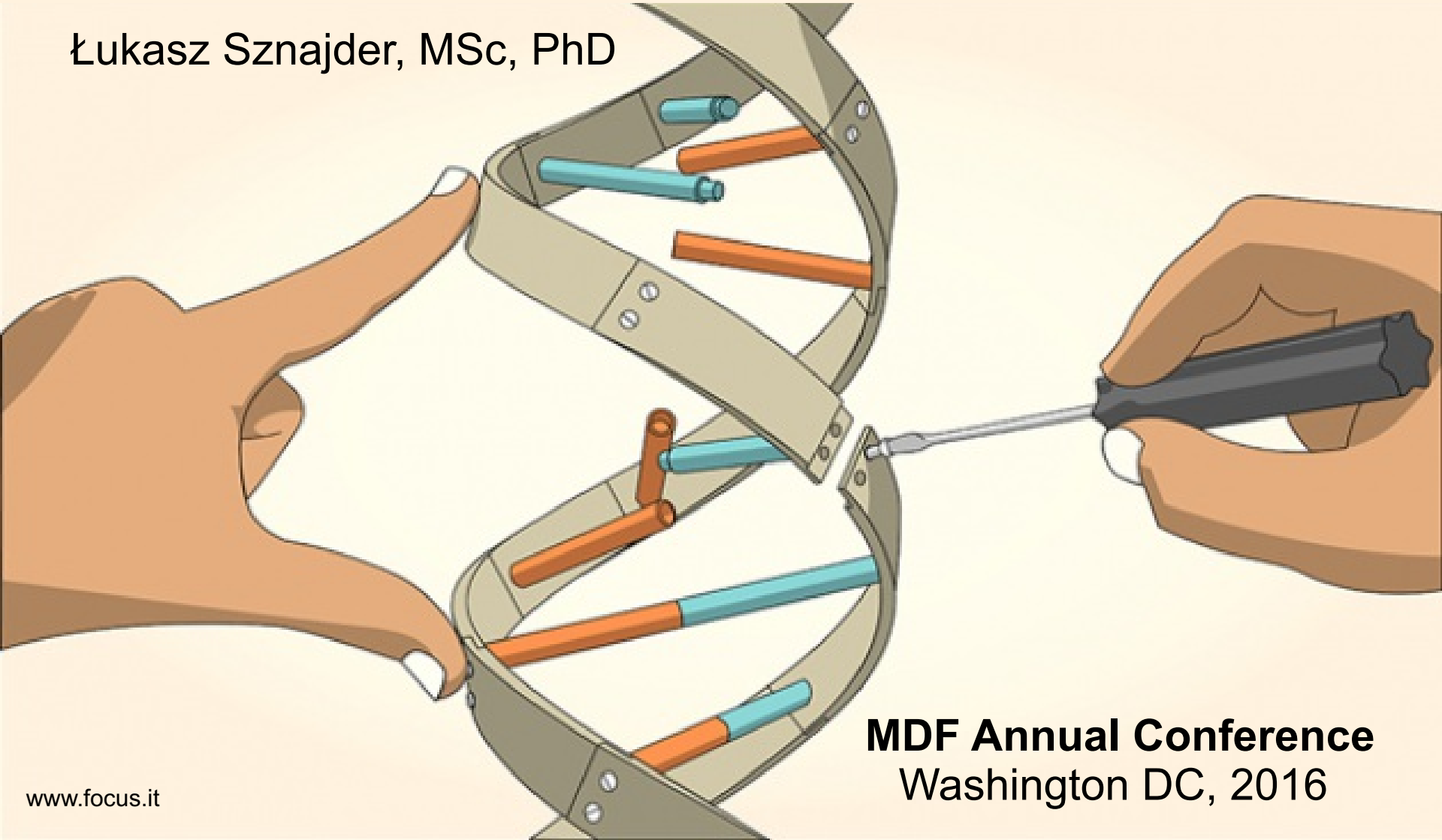
mouse model for DM2

Łukasz Sznajder, MSc, PhD

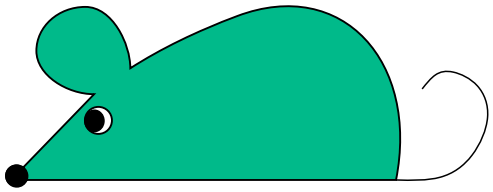


MDF Annual Conference
Washington DC, 2016

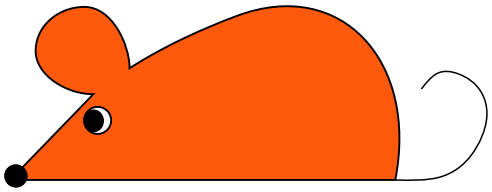
www.focus.it

What is a DM mouse model?

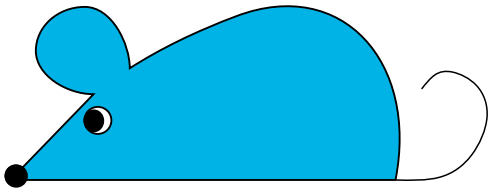
DM mouse models



DM1



DM2



DM1 & 2

Cohort of DM mouse models

What did we learn from models?

C(C)TG repeats expression

***HSA*^{SR}**
$(CTG)_5$
C. Thornton

***HSA*^{LR}**
$(CTG)_{250}$
C. Thornton

EpA0
$(CTG)_0$
T. Cooper

EpA960
$(CTG)_{960}$
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DM20
$(CTG)_{20}$
G. Gourdon

DM55
$(CTG)_{55}$
G. Gourdon

DM300
$(CTG)_{300}$
G. Gourdon

DMSXL
$(CTG)_{1000}$-$(CTG)_{1800}$
G. Gourdon

***GFP-DMPK-*(CTG)$_5$**
M. Mahadevan

***GFP-DMPK-*(CTG)$_{200}$**
M. Mahadevan

***GFP-DMPK-*(CTG)$_{11}$**
R. Korneluk

***GFP-DMPK-*(CTG)$_{91}$**
R. Korneluk

Tg26
$(CTG)_{11}$
B. Wieringa

***Dmpk*(CTG)$_{84}$**
B. Wieringa

***Dmt*-D**
$(CTG)_{162}$
D. Monckton

RNA with CUG expansion is toxic for mouse.

Gene deletion in DM *loci*

***Dmpk*$^{-/-}$**
B. Wieringa

***Dmpk*$^{-/-}$**
S. Reddy

***Six*$^{-/-}$**
S. Reddy

***Six*$^{-/-}$**
S. Tapscott

***Znf9*$^{+/-}$**
Y. Li

***Mbnl* deletion & CELF1 increase**

***Mbnl1*$^{\Delta E3/\Delta E3}$**
M. Swanson

***Mbnl2*$^{-/-}$**
F. Chen

***Mbnl2*$^{\Delta E2/\Delta E2}$**
M. Swanson

***Mbnl1*$^{\Delta E3/\Delta E3}$*+2*$^{c/c}$**
M. Swanson

***Mbnl3*$^{\Delta E2}$**
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***Mbnl3*$^{\Delta E2}$**
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Mbnl3$^{\Delta E2}$
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Crucial RNA metabolism regulators are involved

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Efficiency and toxicity of therapeutics

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What specific about DM2?

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Not much!

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Mouse models relevant for

DM1 DM2 DM1 and 2

Urgent needs in the DM2 field

Why does DM2 have different onset, but also main symptoms as DM1?

Are DM2 and DM1 similar diseases in terms of molecular pathomechanism?

What is a rational therapeutic strategy for DM2?

We must generate DM2 mouse model!

ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ

UF UNIVERSITY of FLORIDA

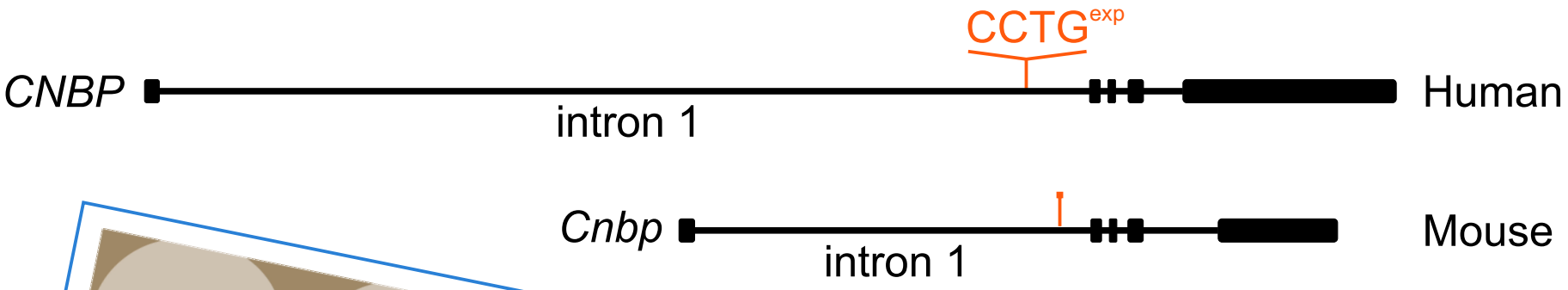
MYOTONIC DYSTROPHY FOUNDATION

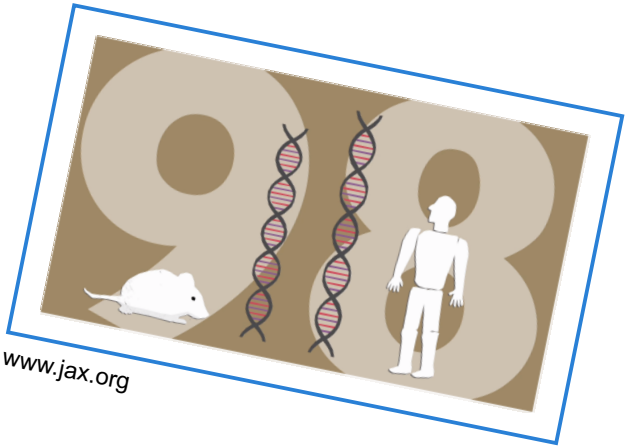
Care and a Cure

Myotonic Myotonic Dystrophy Type 2 Mouse Models, Pathomechanism and Therapy

Experimental strategy

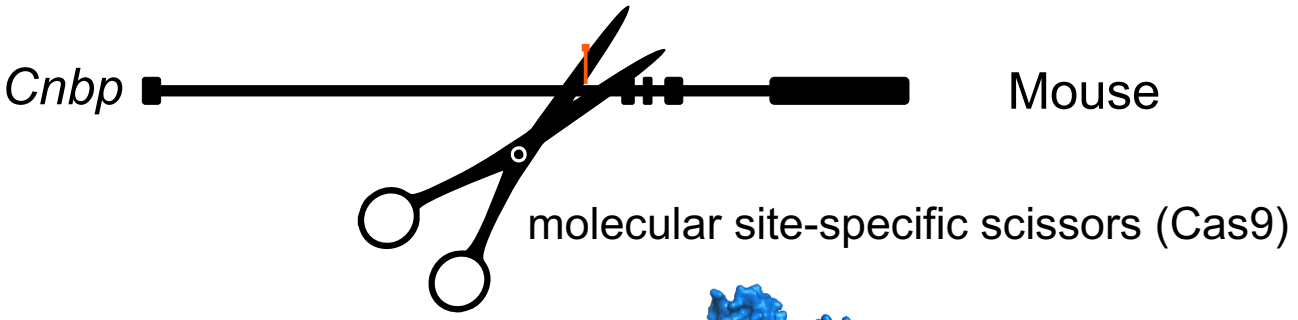
1. Chose the right place in the mouse *Cnbp* gene (DNA).

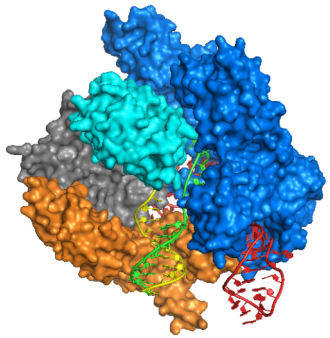




Experimental strategy

2. Cut *Cnbp* gene in appropriate place with molecular scissors.





Anders et al, Nature 2014

Experimental strategy

3. Deliver appropriate DNA faragment with CCTG mutation.

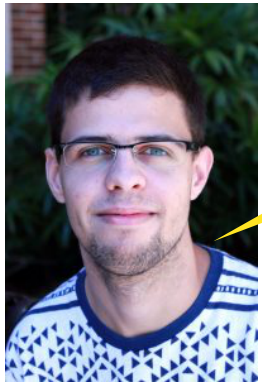
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG

Experimental strategy

4. CCTG repeats are incorporated into mouse *Cnbp* gene.

NNNNNNNNNNCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTG
CCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCC
TGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGCCTGNNNNNNNNNNNNNNN

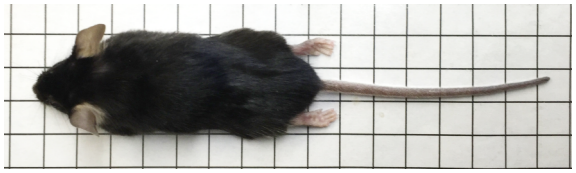
Does it work?



Yes! :-)

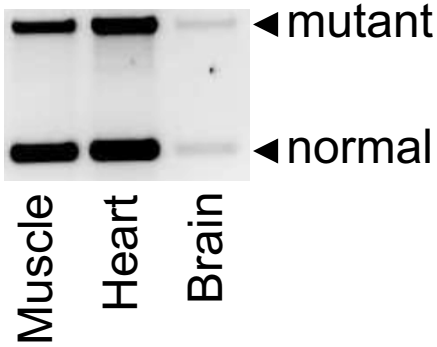
Ruan Oliveria
(PhD candidate
in Swanson Lab)

Novel DM1 mouse model

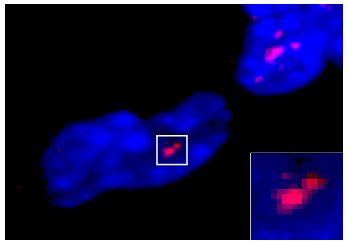


***Dmpk* DNA**

***Dmpk* RNA**



RNA foci

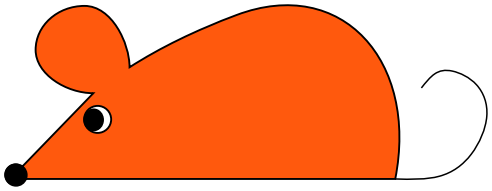


CUG repeats

This mouse model is under intense investigation!

Future perspectives

DM2 mouse model in 2016/2017



DM2

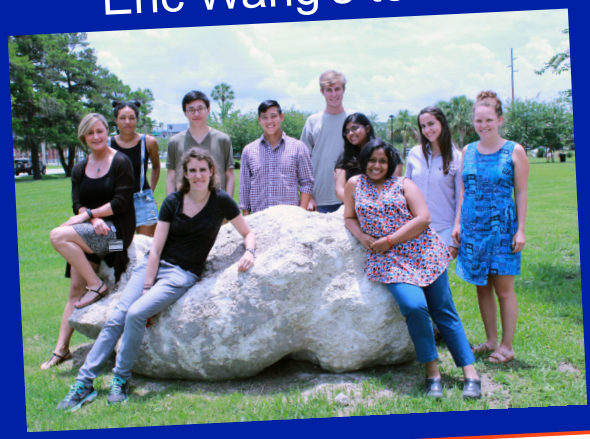
UF | UNIVERSITY of FLORIDA

Maurice Swanson's team

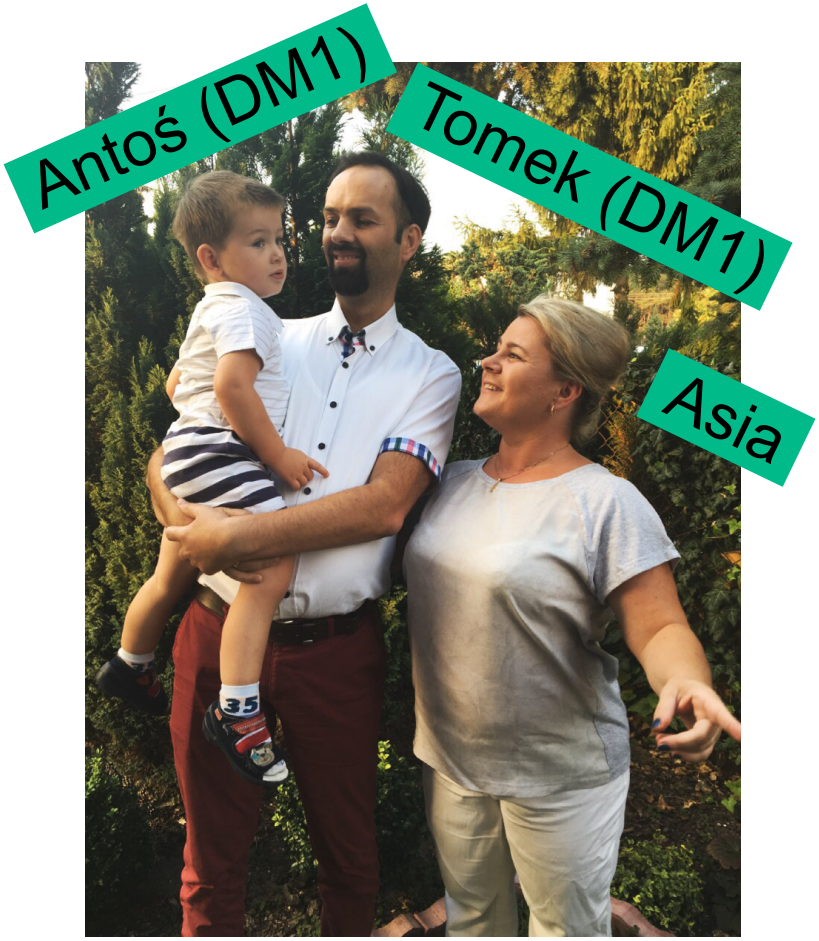
Laura Ranum's team

Andy Berglund's team

Eric Wang's team



DM in Poland



Poles 37,394,000

DM1 490 (1/76.000)

DM2 318 (1/118.000)

We are starting from the scratch!

POZnan
Thank You!