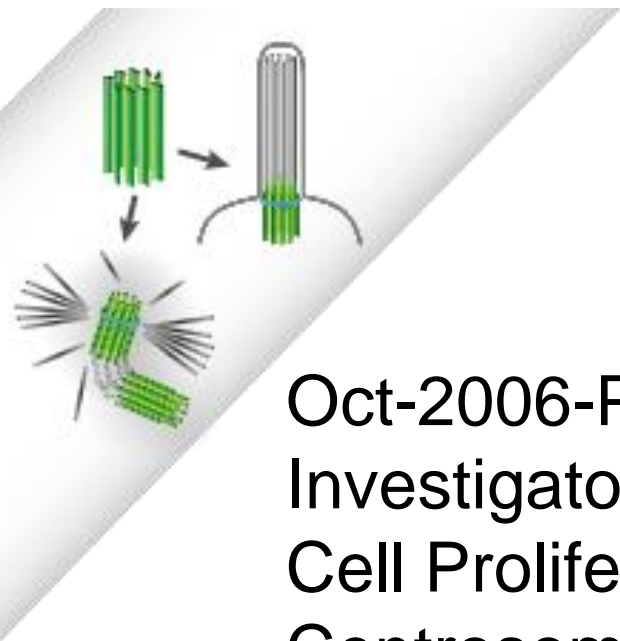




1997-2001-PhD- Cell Biology of Heart Regeneration, Prof. J Brockes, University College London, UK



2002-2006-Post-doctoral research- Regulation of Cell Proliferation, Prof. D Glover, University of Cambridge, UK + Diploma Sci. Com. Birkbeck College, UK



Oct-2006-Principal Investigator-Regulation of Cell Proliferation & Centrosome Assembly, Instituto Gulbenkian de Ciência, Portugal



32 nationalities



400 people, 41 research groups,
3 HHMI young Investigators,
10 ERC Grantees, 2 HFSP grantees,
artists in residence (pianist/composer;
writer; plastic arts), 1 cat & 2 ducks,

2 PhD programs



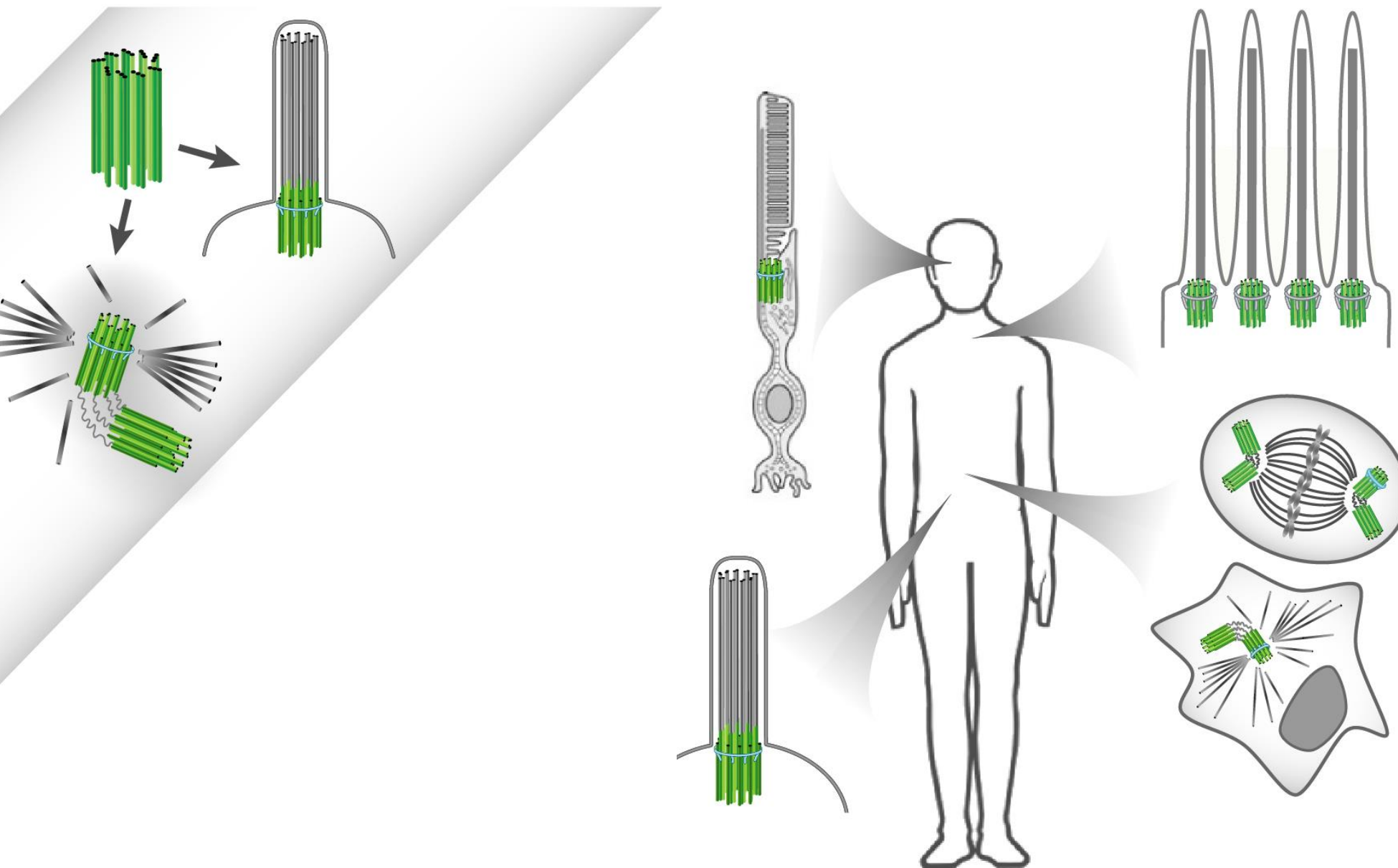
CELL & DEVELOPMENTAL BIOLOGY, EVOLUTION, HOST-PATHOGEN,
DISEASE GENETICS, NEUROSCIENCES, IMMUNOLOGY, EPIDEMIOLOGY
THEORETICAL AND COMPUTATIONAL BIOLOGY

Centrosome Biogenesis

Mónica Bettencourt Dias - Jitu Mayor

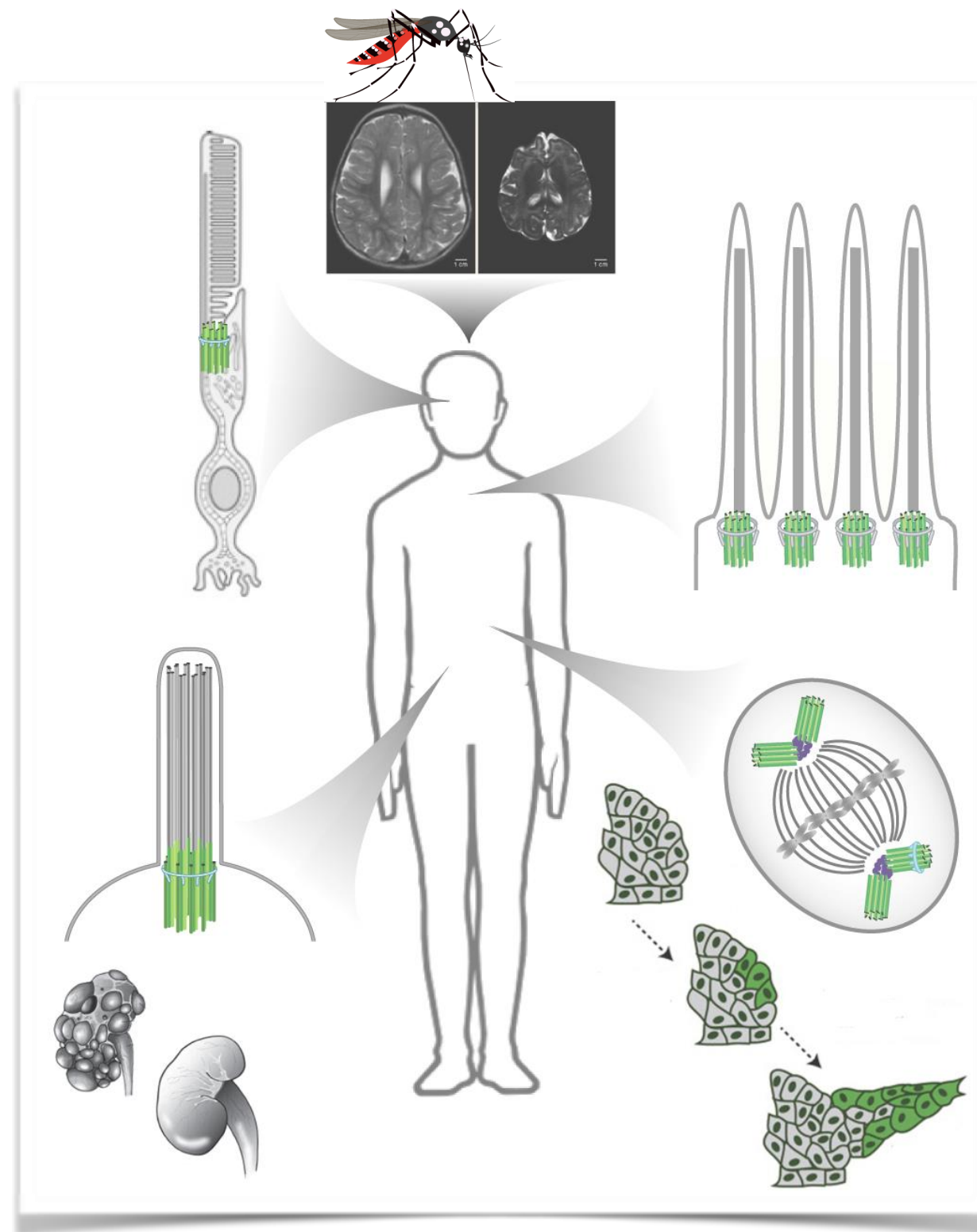
Ivo Telley, Catarina Nabais, Swadhin Jana, Gaelle Marteil,
Thomas van Zanten

Instituto Gulbenkian de Ciência, Oeiras;
National Center for Biological Sciences, Bangalore



Centriole & Centrosomes in Disease

altered structure and/or number
(centrosome amplification)



Labs of: Gopalakrishnan, Gonczy, Nigg, Basto, Raff, Holland, Cleveland, Glover, Pazour, Blainpain, Cimini, Rieder, Fukasawa, Gergely, Wood, Walsh, Jackson

What Triggers Centriole Formation?

19th/20th
century

Beneden



Boveri

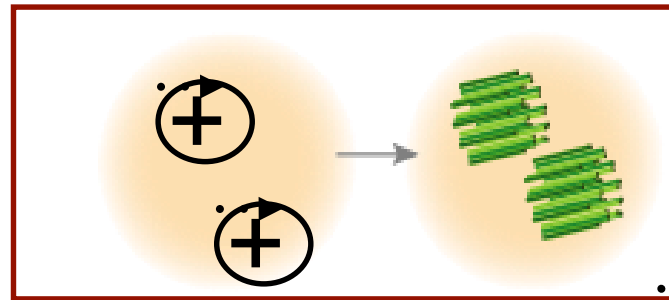
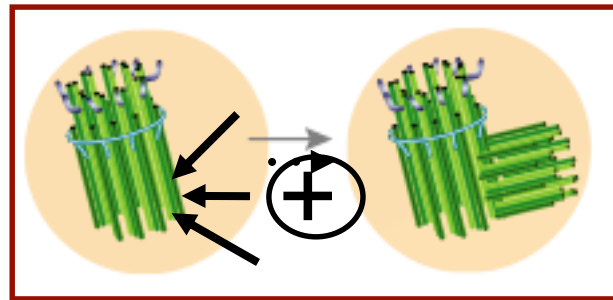
Morgan



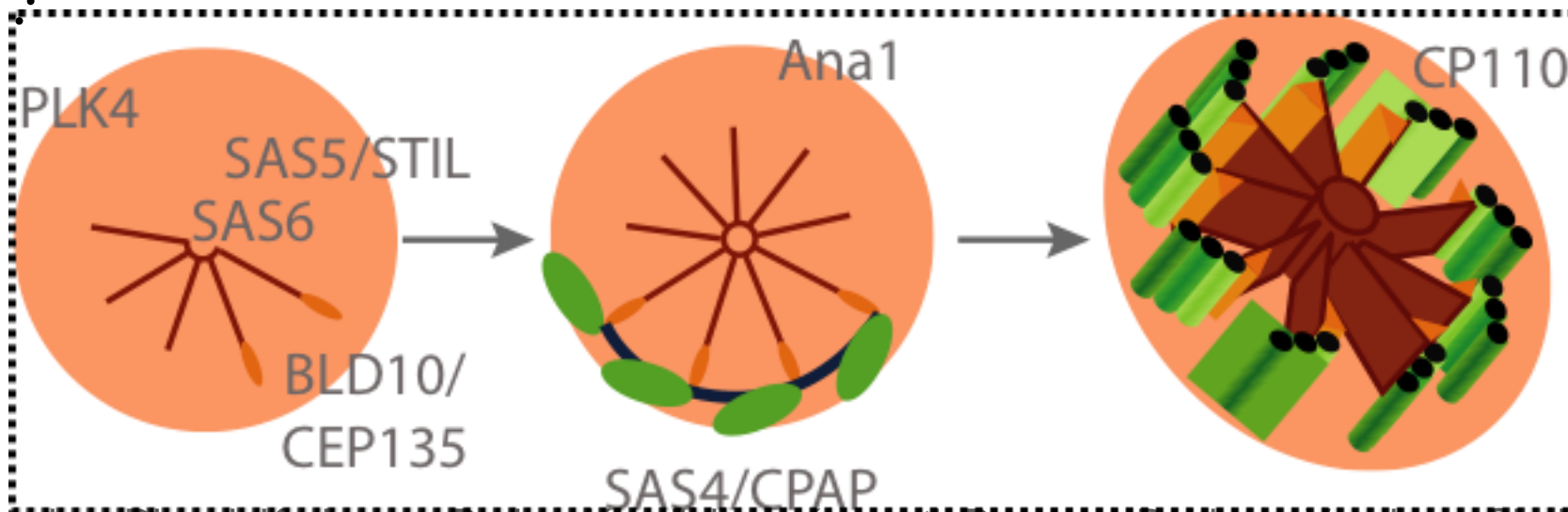
Loeb

CENTROSOME DUPLICATES
AND IS INHERITED

CENTROSOME FORMS
DE NOVO



same machinery: centrioles self assemble
centriole as a catalyst for centriole biogenesis

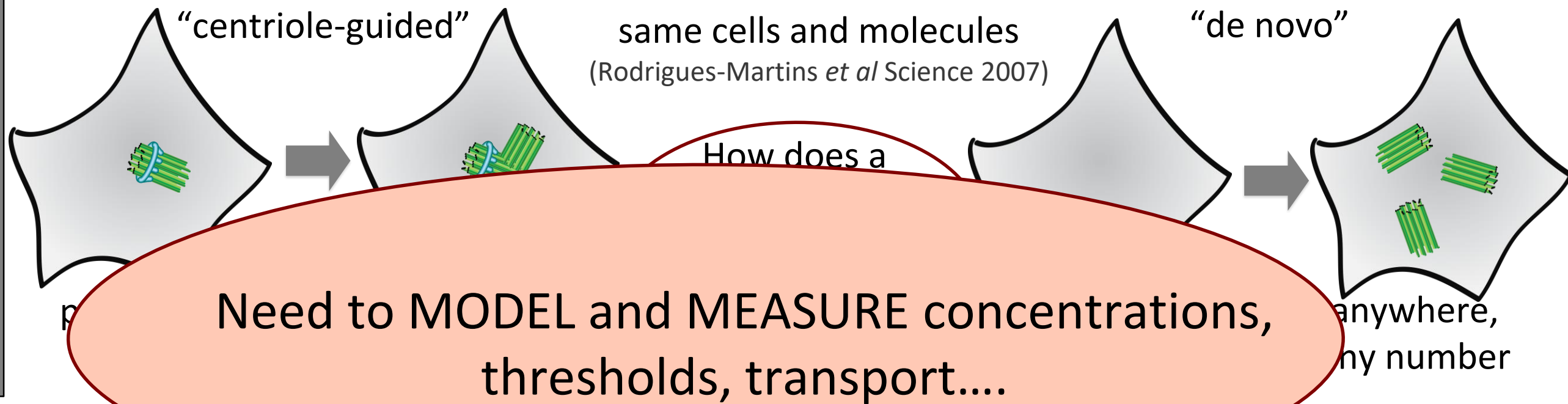


SAS6 SAS4
PLK4
Asl Bld10

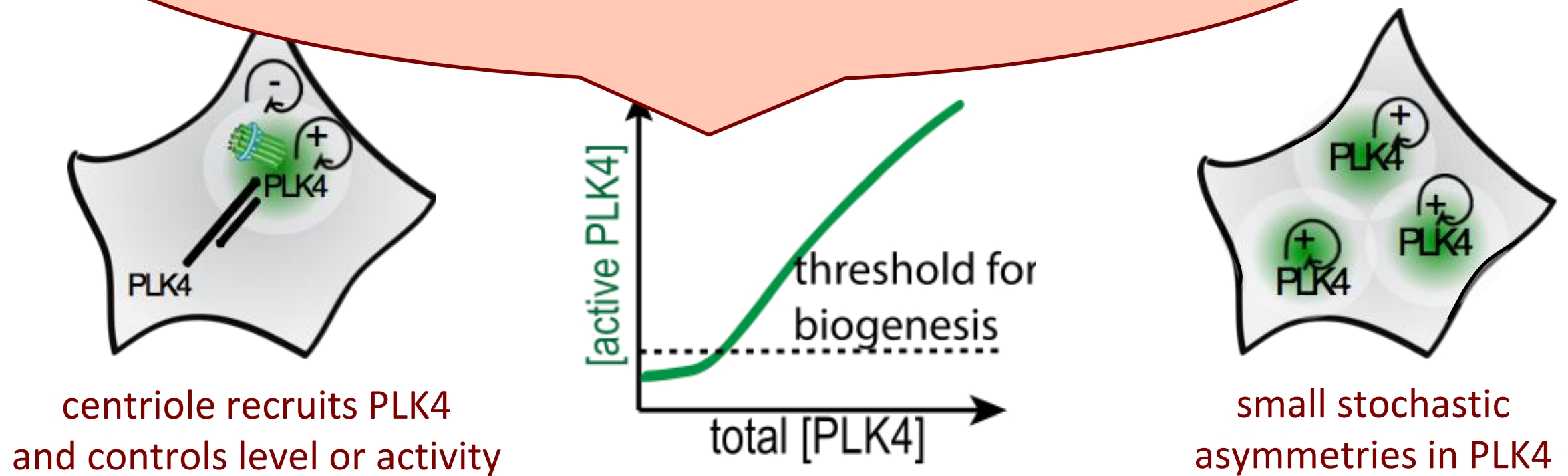
discovered
in last 10-15
yrs

Birth: Right Place

QUESTION



HYPOTHESIS

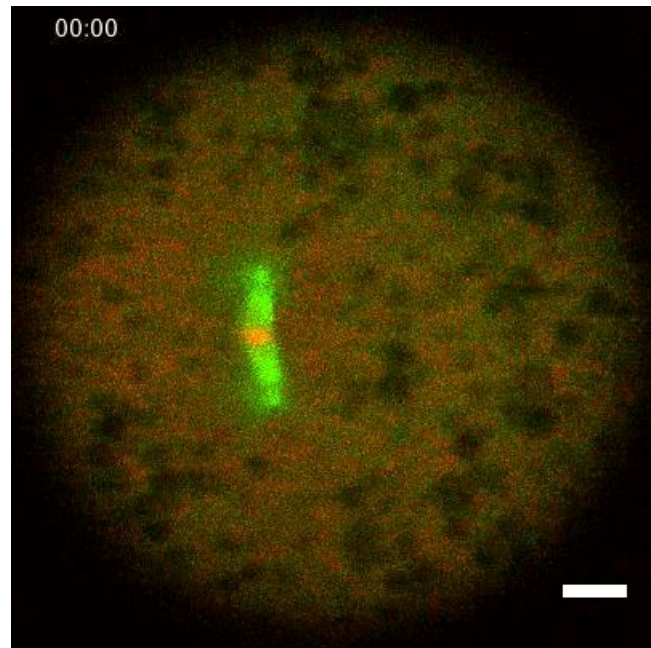


Right Place-Approach

Centrosome Assembly In A Droplet Of A Fly Egg

Unique Droplet System

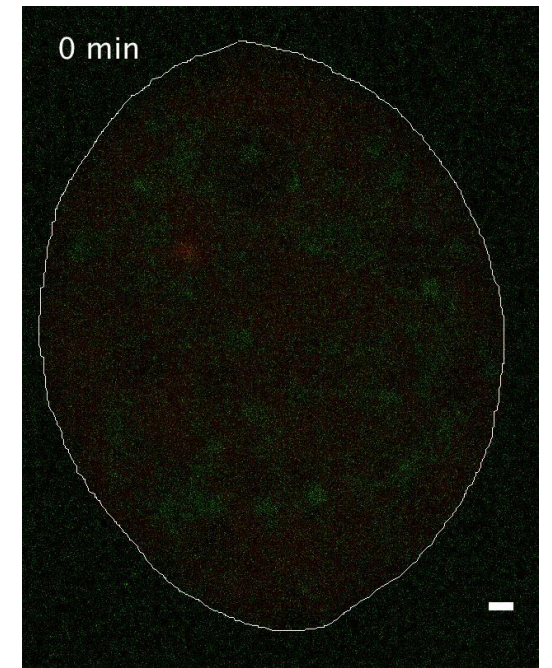
Telley et al, 2013



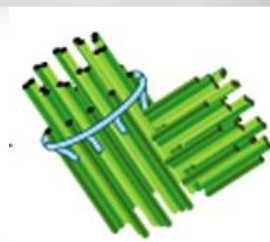
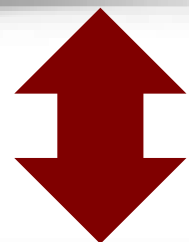
DNA, Microtubules

MEASURE

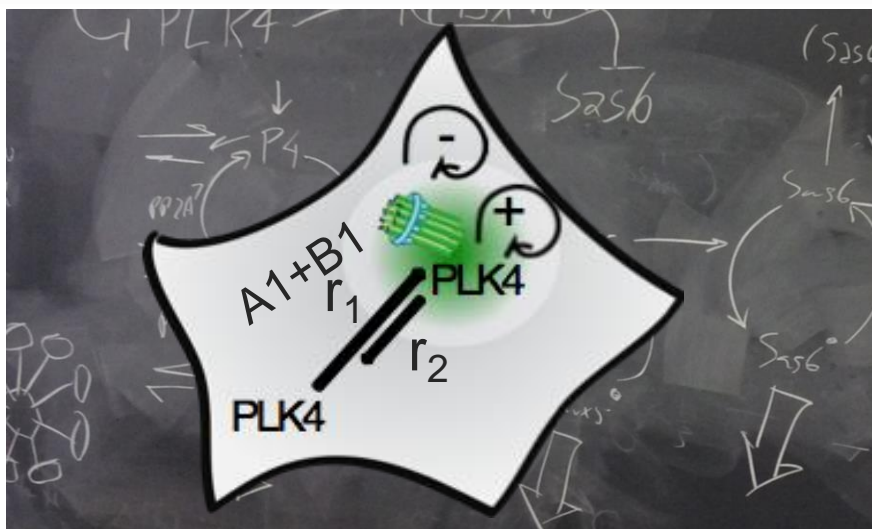
- endogenous PLK4
- transport in mutants, with drugs
- add PLK4 –titrate PLK4 needed for centriole formation (extract with/without centrioles)



Microtubules, Centrioles, +PLK4



In Silico Model



Identify Critical Variables
Raise/Discard Hypotheses

$$\frac{dB_1}{dt} = s - dB_1 - aB_1A_1 - bB_1^2 + pA_1^* + pr_2B_2 - r_1B_1$$

$$\frac{dA_1^*}{dt} = aB_1A_1 + bB_1^2 - cA_1A_1^* + pA_1^{**} - pA_1^* - dA_1^* + pr_2A_2^* - r_1A_1^*$$

How to quantitate? This Project



Ivo Telley



Catarina Nabais



Swadhin
Jana



Gaelle
Marteil

IGC



Jitu Mayor



Thomas van Zanten

FLUORESCENCE CORRELATION SPECTROSCOPY (FCS) MEASURE:

- *endogenous concentration
- *oligomerization
- *diffusion (simple vs directed vs confined)
- *spatio-temporal distribution

Advantages

“Live” measurements
Single-molecule sensitivity
Good for low abundance proteins

Limitations

Not an imaging technique
Limited to some μm into the sample
Complex data analysis!!!!

NCBS

Why this group?



Jitu Mayor

Expert: protein trafficking; membrane dynamics;
quantitative fluorescence microscopy
“revealed the nanoscale landscape of the
mammalian plasma membrane”

Senior Professor and Director at National Centre for
Biological Sciences Tata Institute for
Fundamental Research, and the Institute for Stem Cell
Biology and Regenerative Medicine in Bangalore, India.

Many Grants and awards:

2016-Margadarshi Fellowship, Wellcome

Trust DBT Alliance Award, 2015-Foreign Associate of the US
National Academy of Sciences, 2013-Distinguished Alumnus of
IIT Mumbai, 2013-Elected EMBO Fellow, the 2012-Infosys Prize
for Life Sciences, the 2010-TWAS Prize in Biology, the 2006
and 2011-JC Bose Fellowship, DST and the 2003-Shanti
SwaroopBhatnagar Award, CSIR.



Thomas van Zanten

Expert in quantitative fluorescence
microscopy

NCBS (Bangalore)



Obaid Siddiqi (started the molecular biology
unit at TIFR, Mumbai, *Drosophilist*) also found
the National Center for Biological Sciences
(NCBS) in Bangalore in 1992, which has
developed into **India's premier biological**
institute. NCBS's also seeded a nearby Stem
Cell Institute

*state-of-the-art microscope and fluores-
cence-activated cell sorter facilities

How did this collaboration start?



Swadhin joined
my group 2012

India “Science Tour”
2012
including NCBS

Interaction Physiology Course
Woods Hole 2012, 2013



Interaction Santa Barbara
Kavli Institute for Theoretical Physics
2015



Centriole Biogenesis- Biological Outcomes

Centrosome Assembly In A Droplet Of A Fly Egg

et al, 2013

00:00

MEASURE:

- endogenous PLK4 (FCS)
- transport (FRAP, FCS)

0 min



UNDERSTANDING

Where and how many centrioles form?

GENERALITY

Similar principles establishing singularities in biology?

DEVIATIONS

How circuits are modified
& deregulated
(other cell types, organisms, disease-e.g. cancer)

Unique Droplet System

In Silico
Modelling

$A_1 + B_1 \xrightarrow{r_1} A_1^* + B_1^*$
 $A_1^* + B_1^* \xrightarrow{r_2} PLK4$

$$\frac{dB_1}{dt} = s - dB_1 - aB_1A_1 - bB_1^2 + pA_1^* + pr_2B_2 - r_1B_1$$
$$\frac{dA_1^*}{dt} = aB_1A_1 + bB_1^2 - cA_1A_1^* + pA_1^{**} - pA_1^* - dA_1^* + pr_2A_2^* - r_1A_1^*$$

PLK4

Pros & Cons of these Partnership Programs

PROS

- *great!
- *expertise
- *equipment
- *cross-culture experience
- *input on work (e.g. thesis)

TO IMPROVE

- *time to decision
- *money that allows for sabbaticals
i.e. longer stays