New therapies and new ideas about Kawasaki disease

Jane C. Burns MD

Rady Children's Hospital San Diego

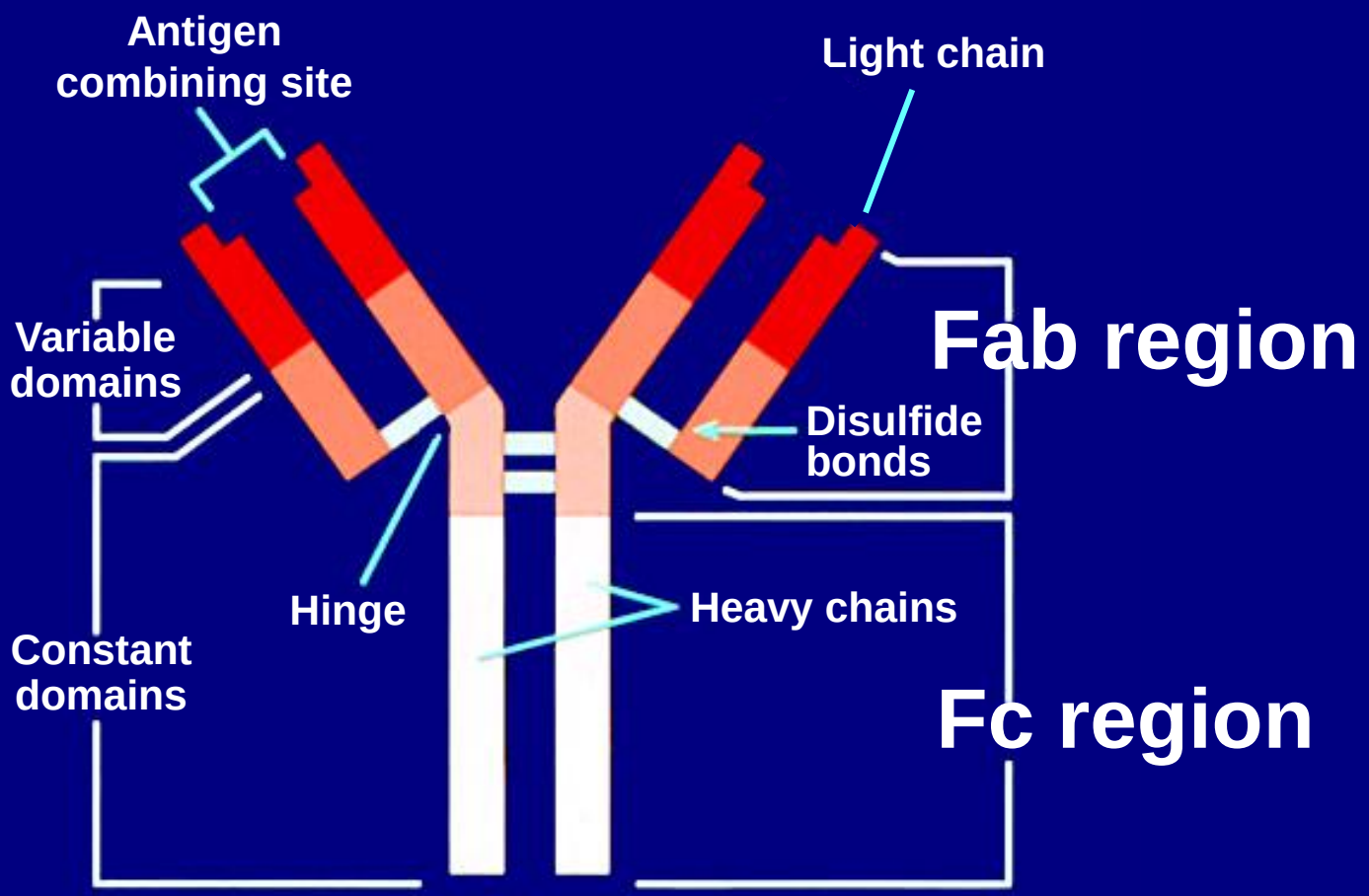
KAWASAKI DISEASE RESEARCH CENTER
RADY CHILDREN'S HOSPITAL/UC SAN DIEGO

UNIVERSITY OF CALIFORNIA · SAN DIEGO ·

Objectives
To review new ideas about…

1. **How IVIG works in KD**
2. **Role of infliximab in KD**
3. **How aneurysms form**
4. **Statins to prevent aneurysms in acute KD**
5. **The trigger that causes KD in genetically susceptible children**

Basic Structure of IgG



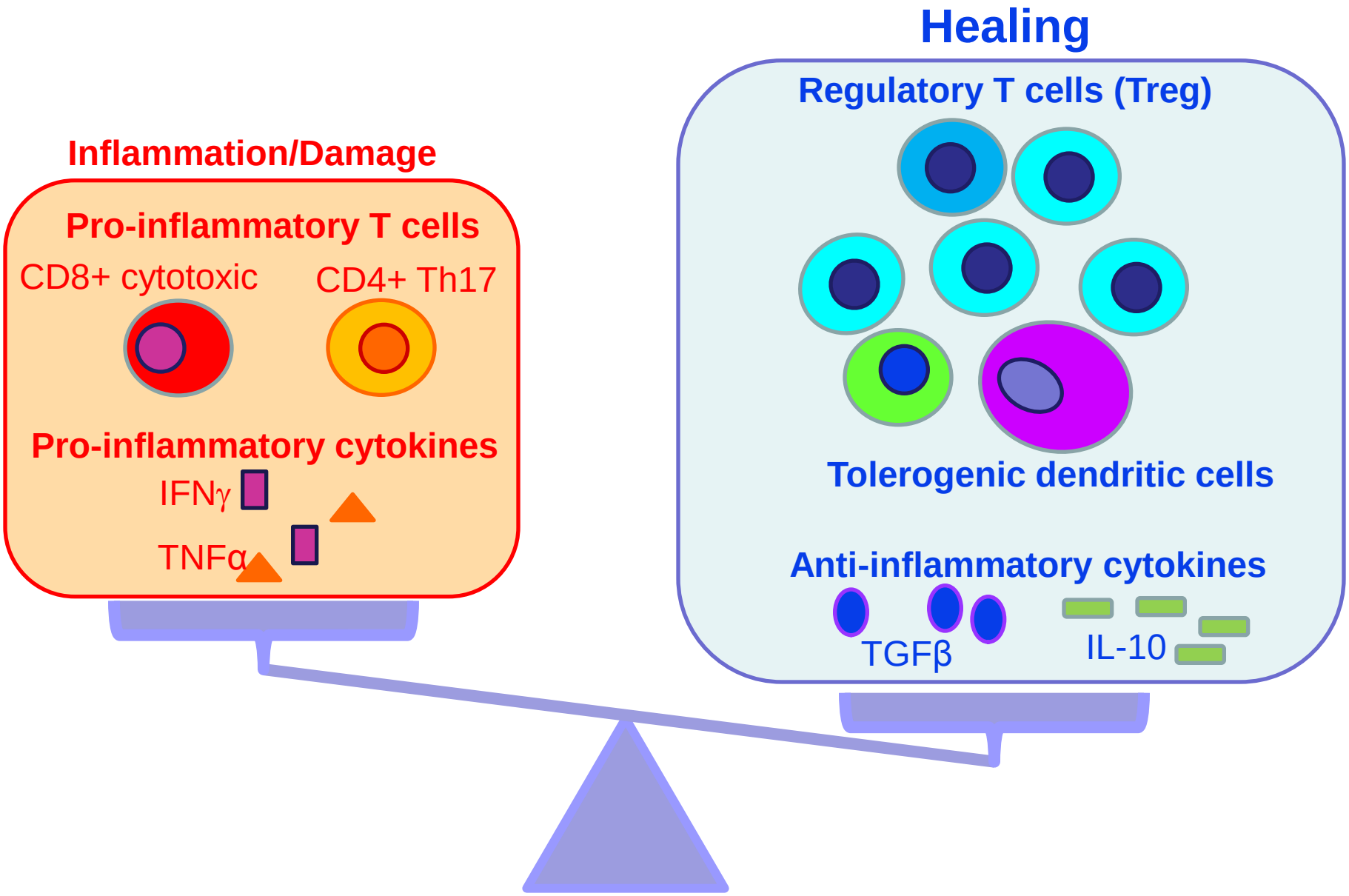
Proposed mechanisms of action of IVIG in KD

F(ab)^2-dependent mechanisms:

1) Anti-cytokine antibody
2) Anti-idiotype antibody
3) Receptor blockade

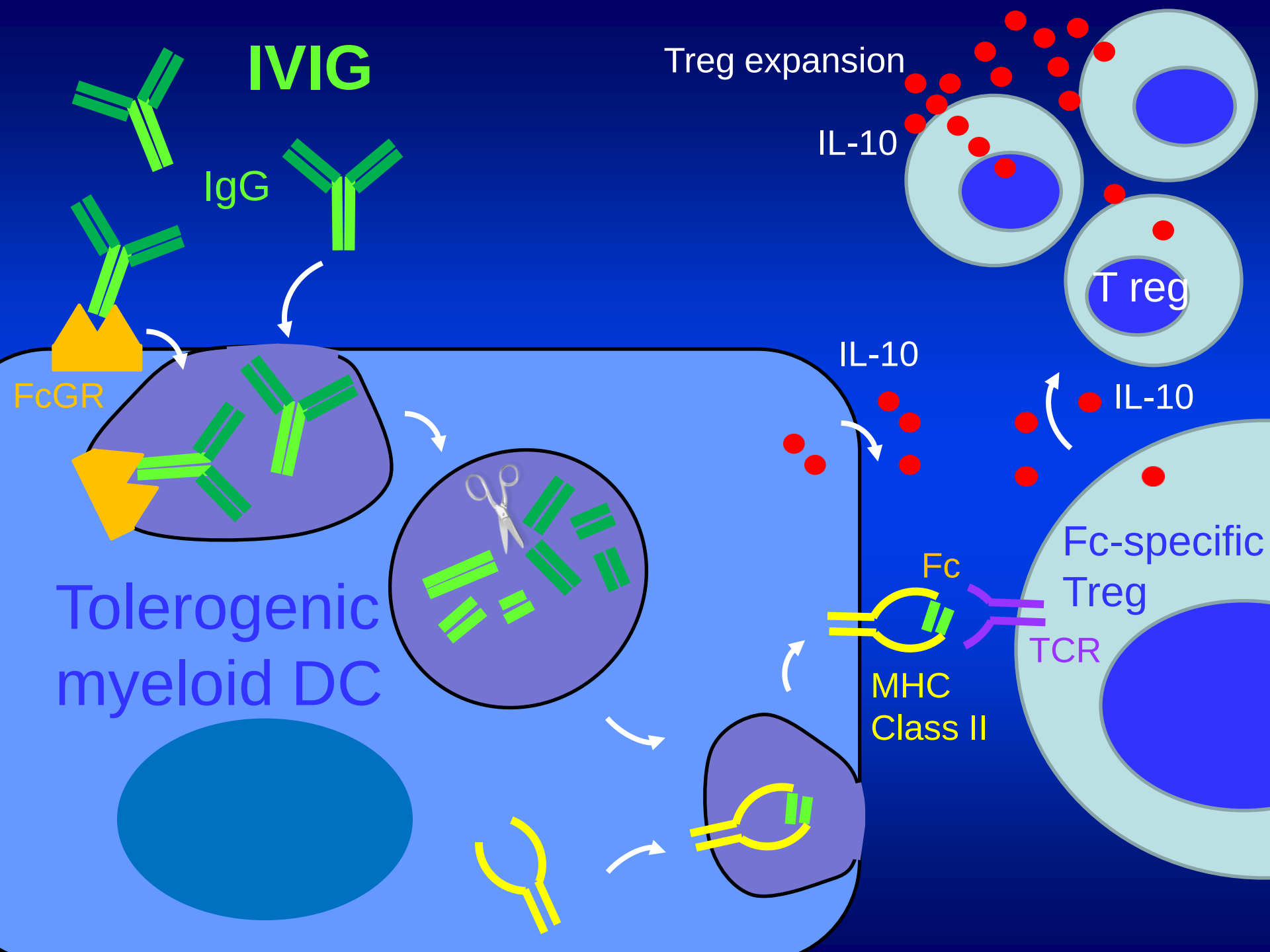
Fc-dependent mechanisms:

1) Cross-linking and stimulating inhibitory FcγRs
2) Blocking activating FcγRs
3) Presentation of Fc peptide to T cells that polarize toward a regulatory phenotype

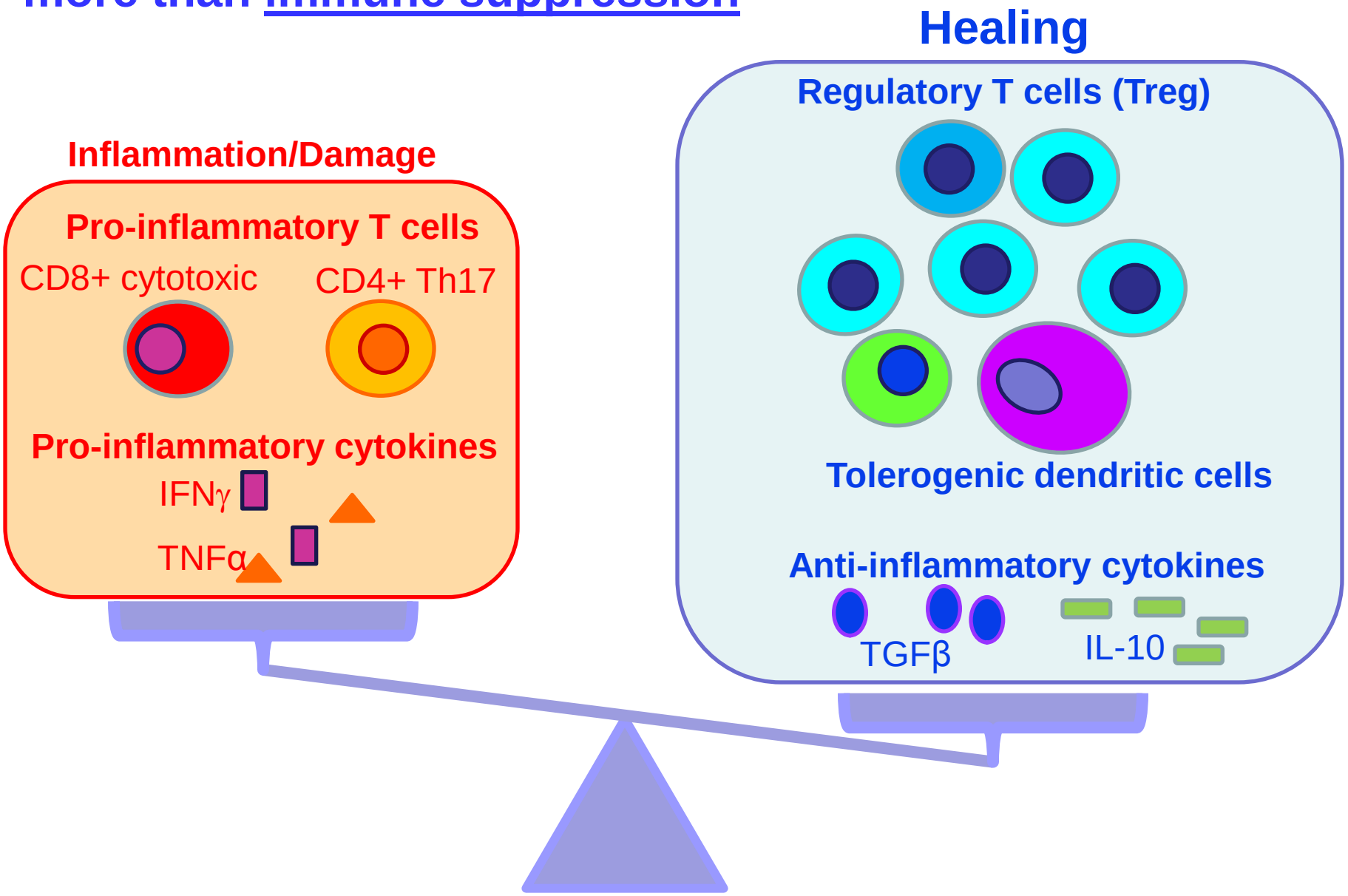

Healing
Regulatory T cells (Treg)
Tolerogenic dendritic cells
Anti-inflammatory cytokines
TGFβ
IL-10
Inflammation/Damage
Pro-inflammatory T cells
CD8+ cytotoxic
CD4+ Th17
Pro-inflammatory cytokines
IFNγ
TNFα

Alessandra Franco MD PhD
UCSD
Collaboration with the
KD Research Center

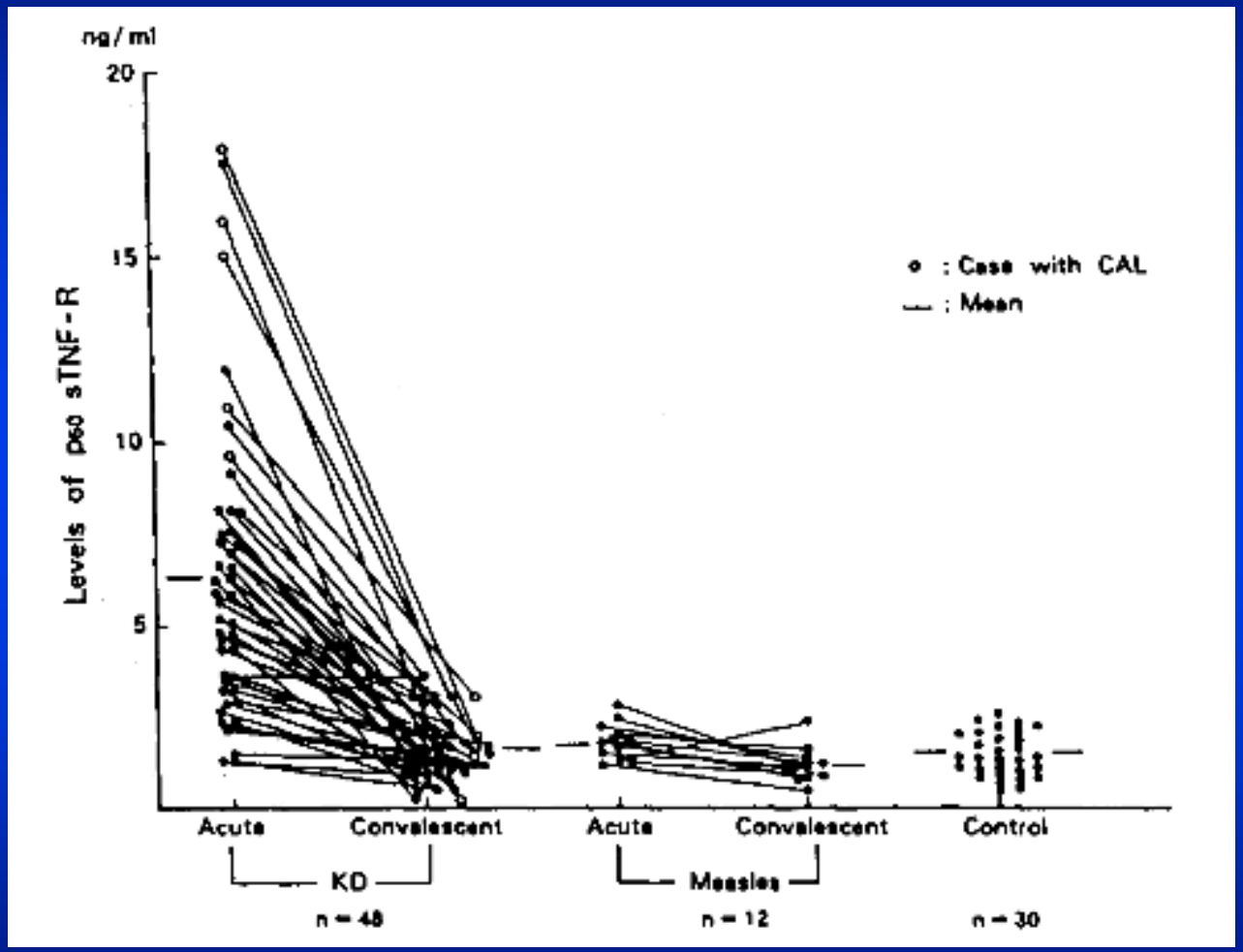
Immune monitoring of KD subjects
before and after treatment


IVIG
IgG
FcGR
Tolerogenic
myeloid DC
Treg expansion
IL-10
T reg
IL-10
IL-10
Fc
MHC
Class II
TCR
Fc-specific
Treg

KD patients need immune regulation more than immune suppression



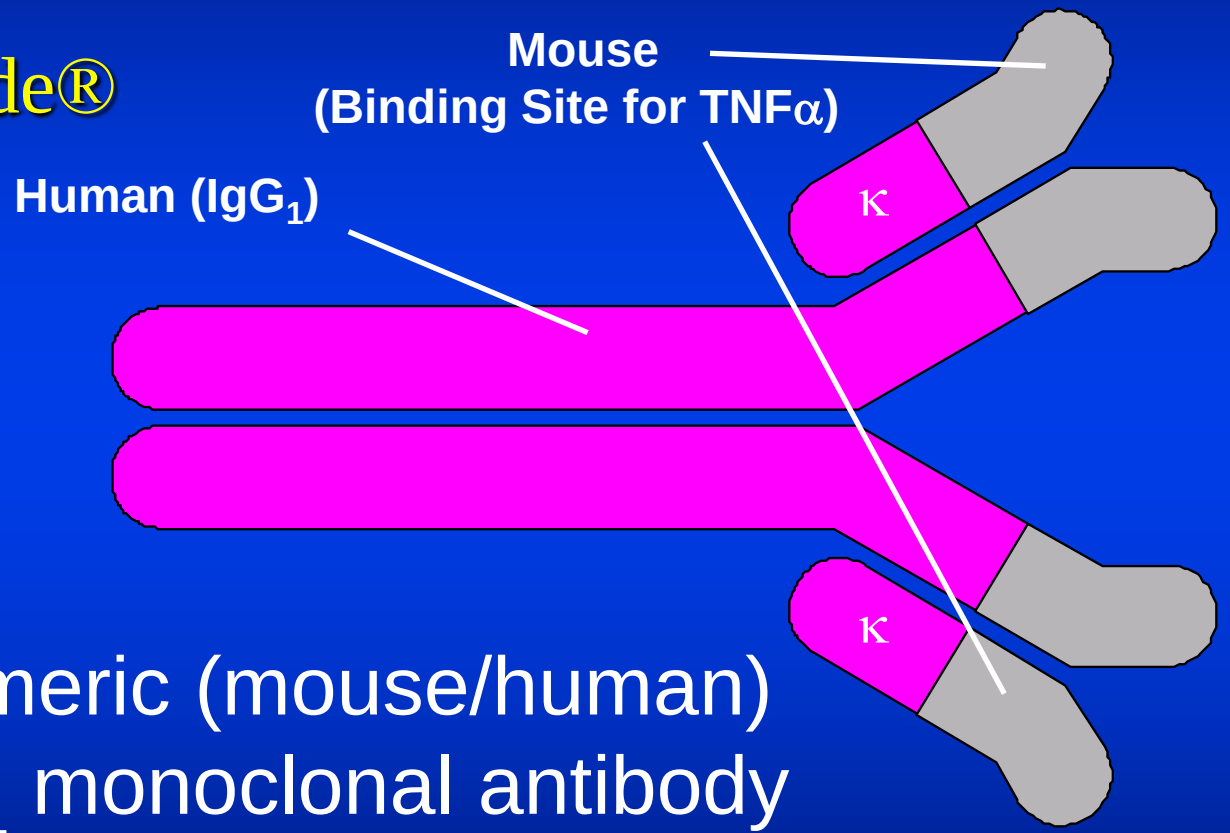
Soluble TNF Receptor Levels in KD



Furukawa et al, J Pediatr. 1994

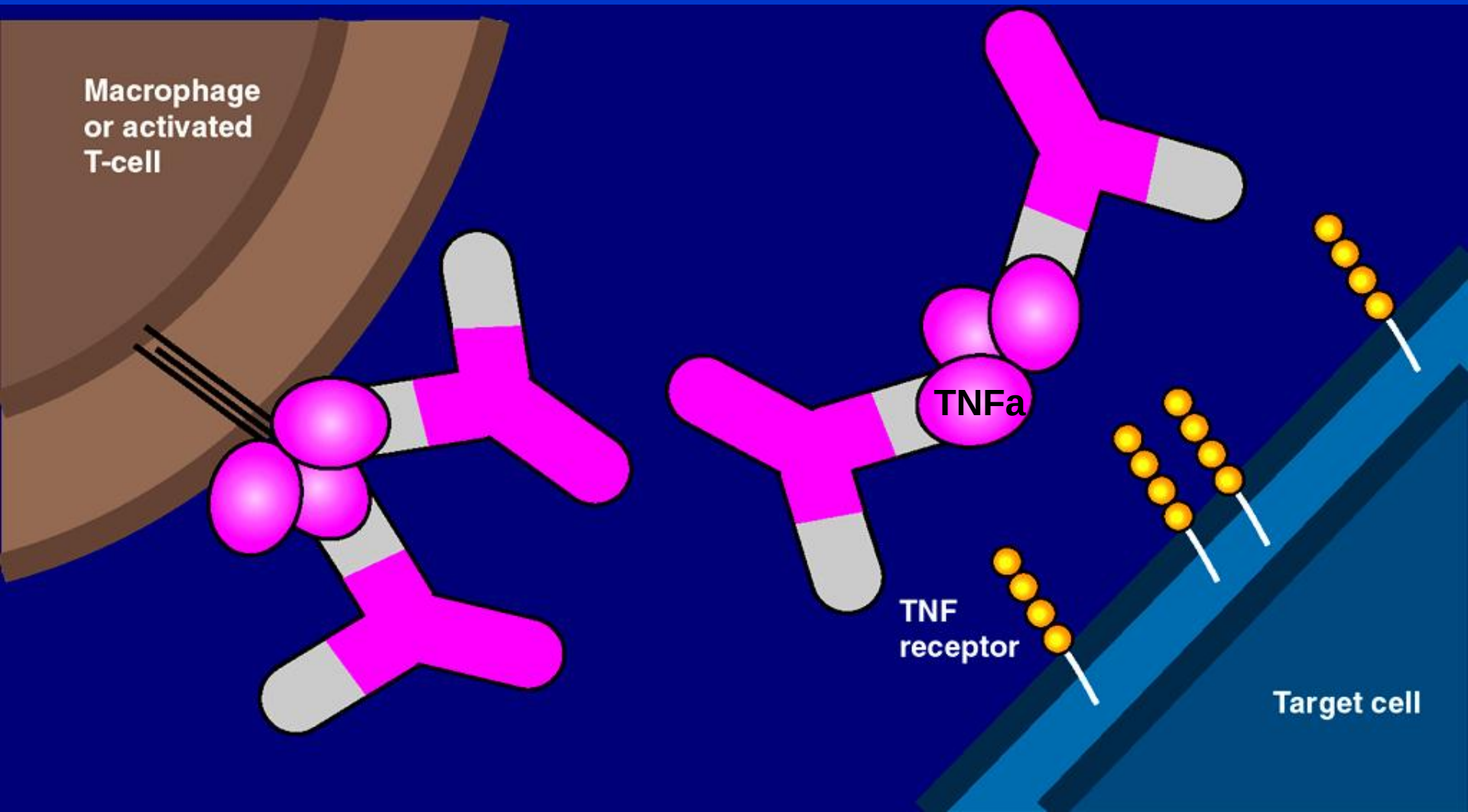
Infliximab: Chimeric monoclonal antibody

Remicade®



- Chimeric (mouse/human) IgG_1 monoclonal antibody
- Binds to TNFα with high affinity and specificity

Antibody neutralization of TNFα



Phase III, randomized, double-blind, placebo-controlled, trial of infliximab + IVIG for initial treatment of KD patients

HYPOTHESIS:

The addition of infliximab to standard IVIG + aspirin therapy will more effectively reduce inflammation in acute KD compared to standard treatment

Primary Outcome

Difference in rates of

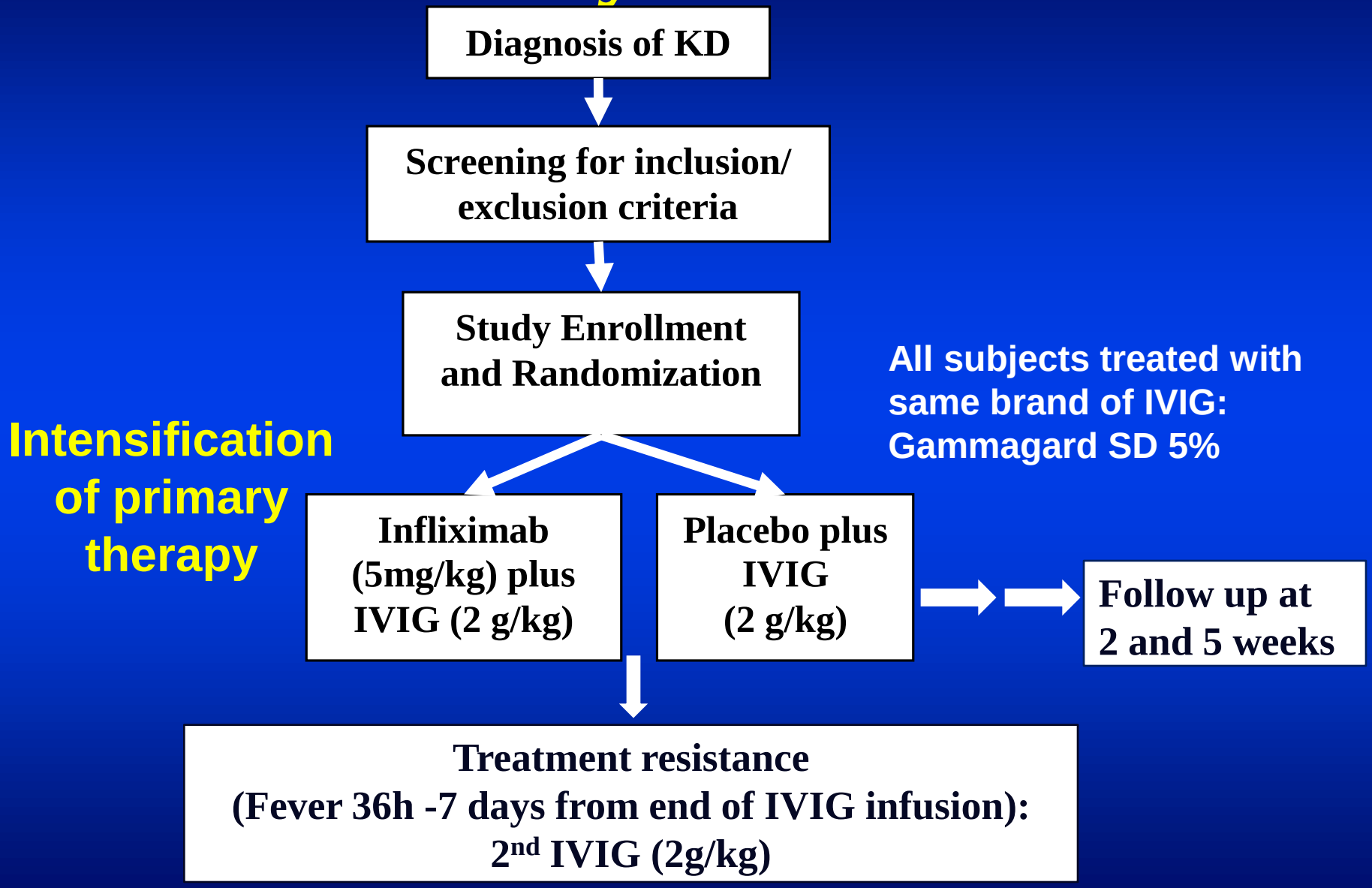
treatment-resistance*

between the placebo + IVIG and infliximab + IVIG groups

***Fever (≥38ºC) 36 hours – 7 days after the end of the 1st IVIG infusion**

- **Sample size (196 subjects) calculated based on 80% power to detect reduction in treatment-resistance from 20% to 5%**

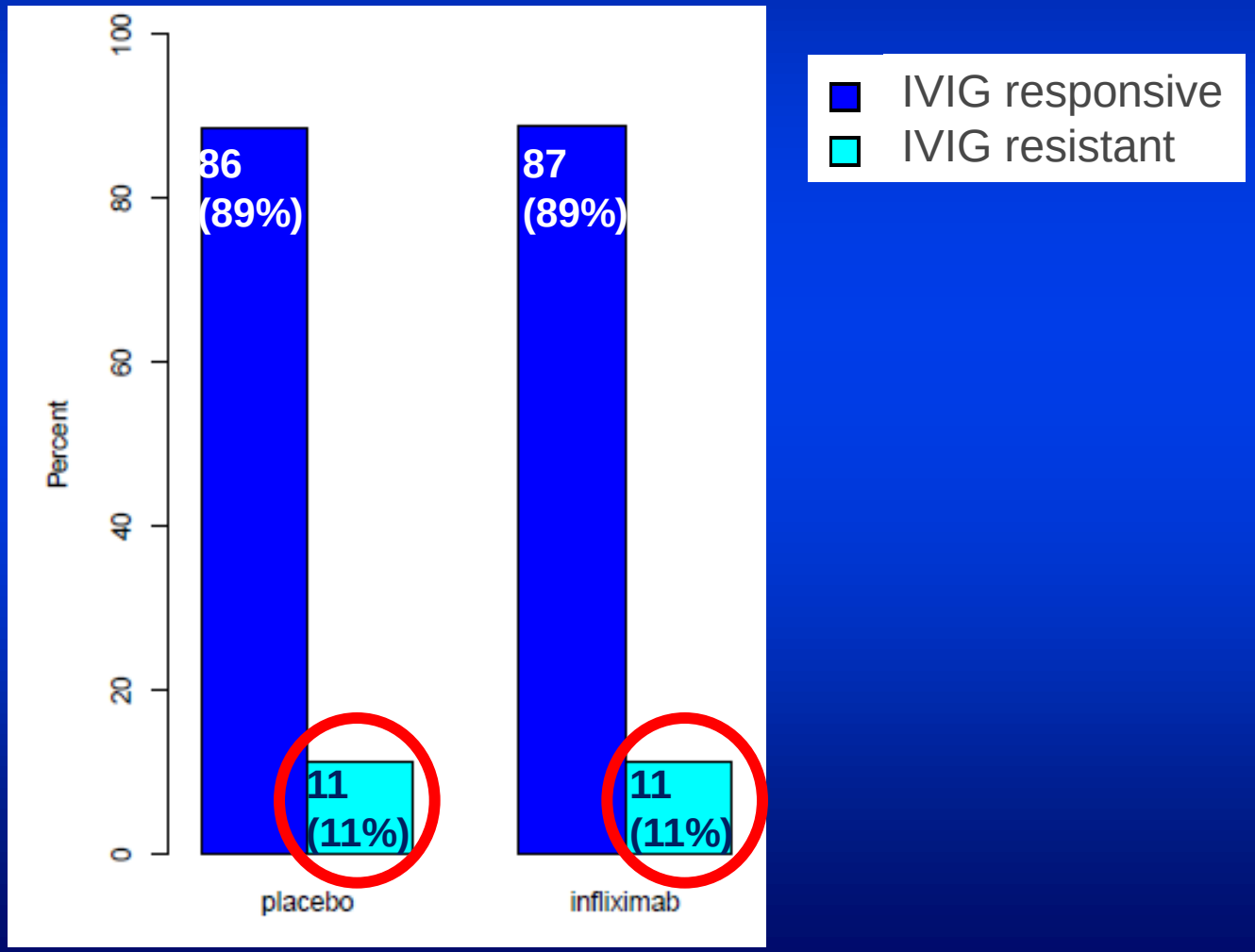
Study Flow


Diagnosis of KD
Screening for inclusion/ exclusion criteria
Study Enrollment and Randomization
All subjects treated with same brand of IVIG: Gammagard SD 5%
Intensification of primary therapy
Infliximab (5mg/kg) plus IVIG (2 g/kg)
Placebo plus IVIG (2 g/kg)
Follow up at 2 and 5 weeks
Treatment resistance (Fever 36h -7 days from end of IVIG infusion): 2nd IVIG (2g/kg)

Primary outcome:

No difference in treatment resistance rate

Fever 36 hours-7days after end of 1st IVIG infusion



Infliximab is safe in KD

- No difference in adverse events between groups
- Tolerated well both in infants and older children
  - 11 infants < 1 yr. received infliximab

Biologic Effect:
Change in mean laboratory values from baseline

	Placebo	Infliximab	P value
Absolute neutrophil count @ 24 hours	-5019	-6108	0.024
C-reactive protein (mg/dL) @ 24 hrs	-3.6	-6.6	<0.0001
Erythrocyte sedimentation rate @ 2 weeks	-14	-23	0.009

Clinical Effect: Days of Fever* Following Enrollment

	Median days	95% CI
Infliximab	1	1-1.4
Placebo	2	1.6-2.1

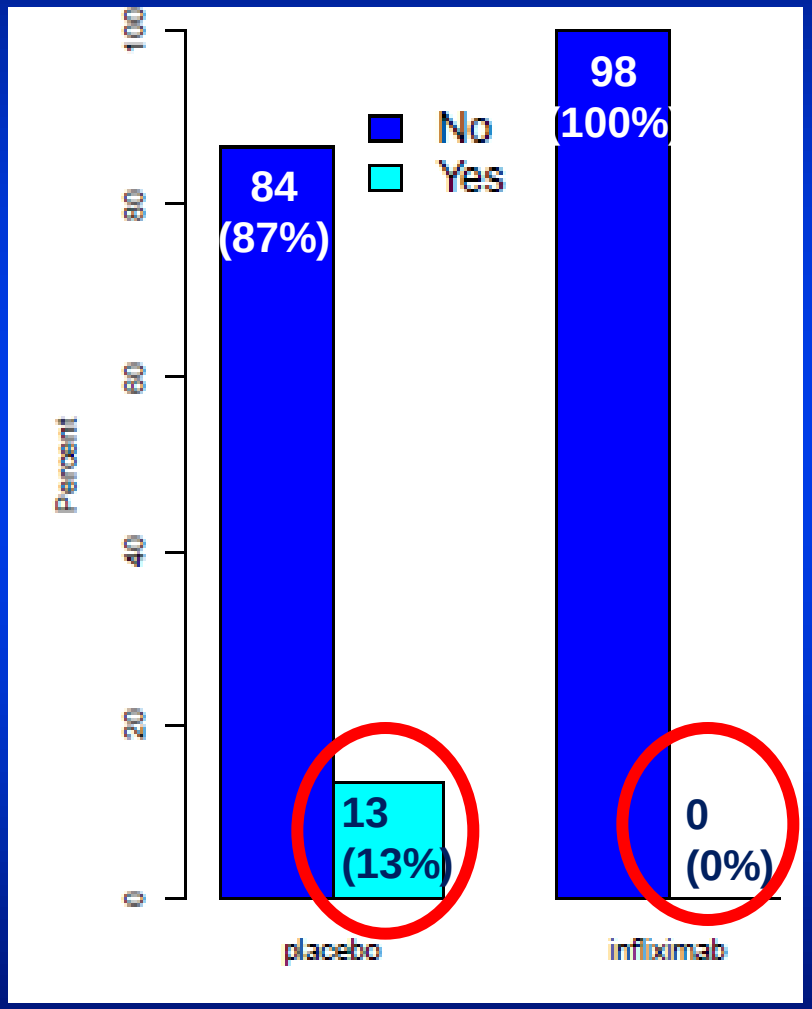
P<0.0001

- **Fever day = any calendar day during hospitalization with T≥38ºC**

Clinical Effect: IVIG Infusion Reaction*

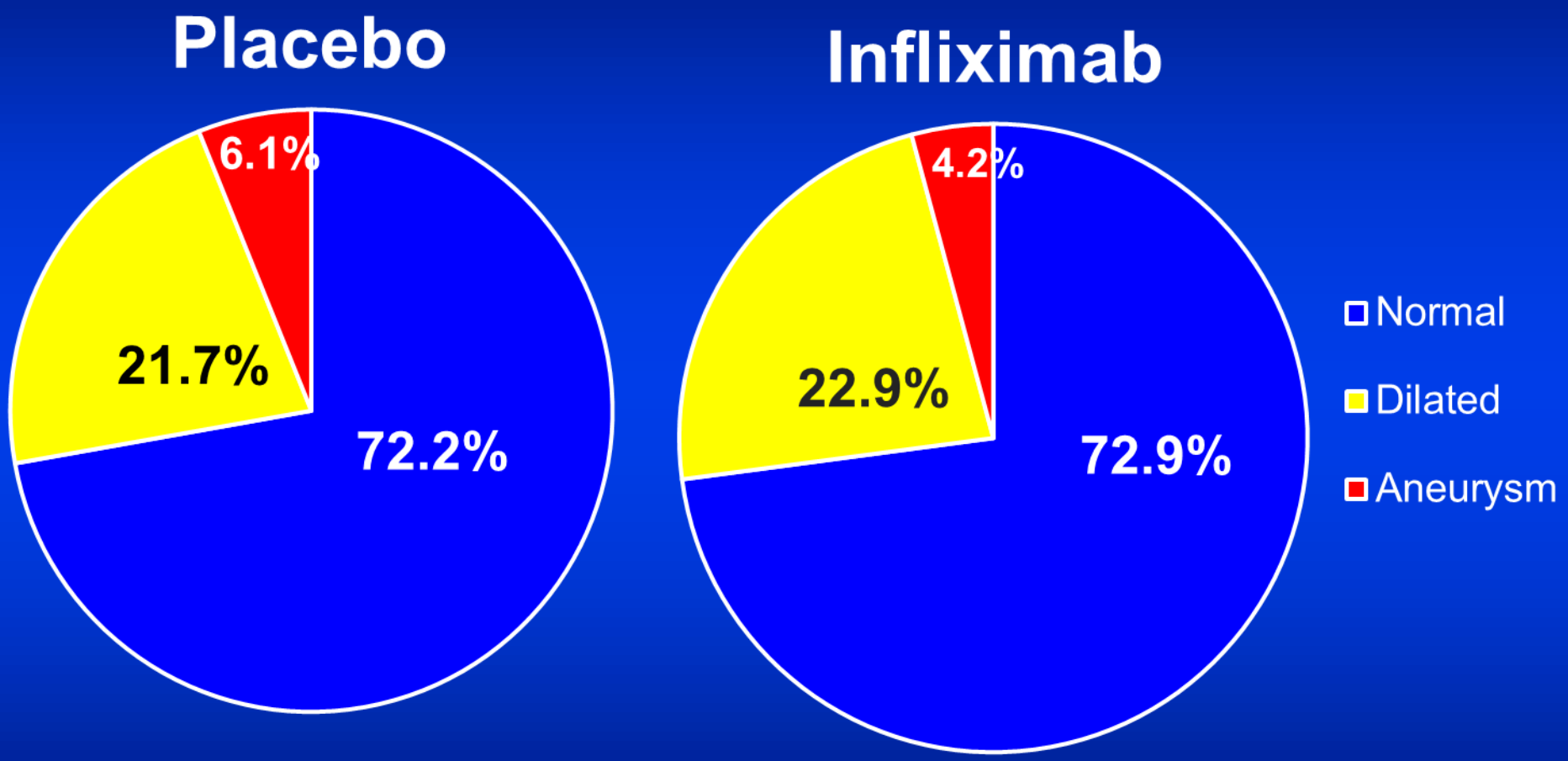
* **Chills or hypotension requiring temporary interruption of IVIG infusion**

- All subjects were pre-medicated with acetaminophen & diphenhydramine prior to study drug



P<0.0001

Clinical Effect: Echo data



All echoes read by a single reader blinded to treatment assignment

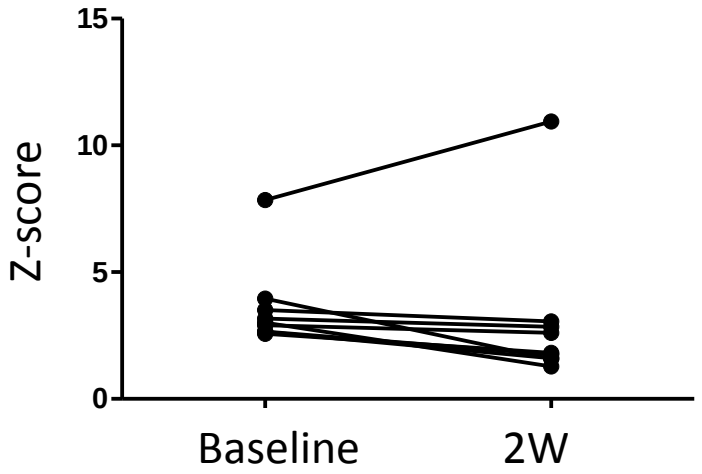
Change in mean LAD Z-score*

	Infliximab	Placebo	P value
Week 2	-0.6	-0.3	0.045
Week 5	-0.8	-0.5	NS

*Z score = standard deviations from the mean internal diameter adjusted for body surface area
NS = not significant

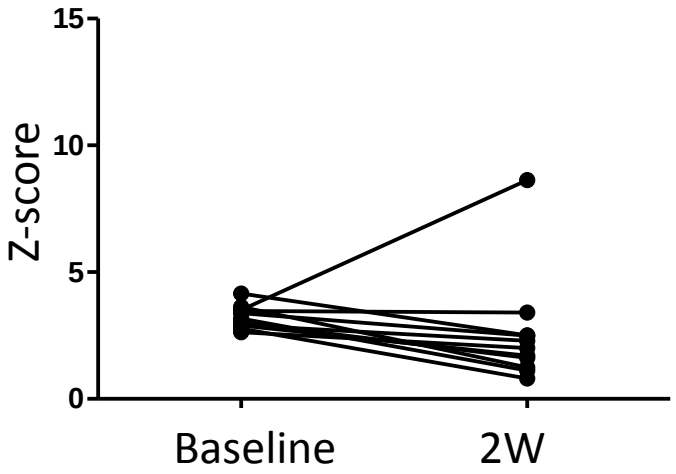
INFLIXIMAB + IVIG

RCA Z-score>2.5 only

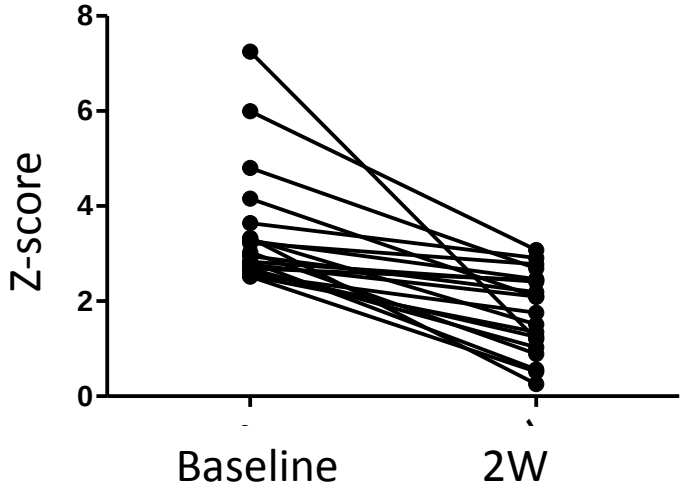


PLACEBO + IVIG

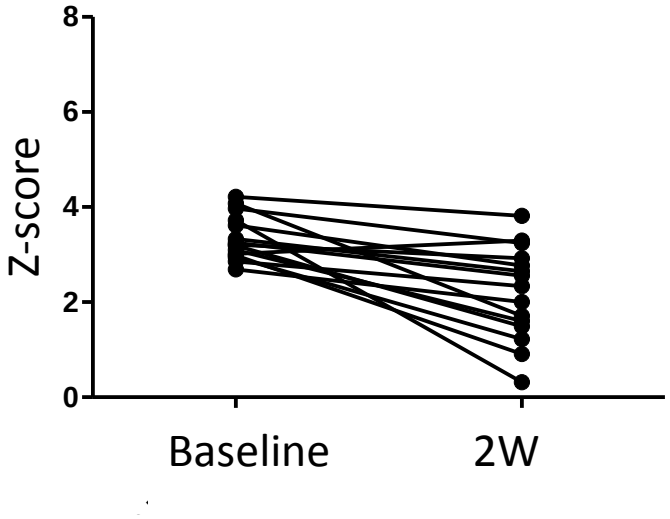
RCA Z-score>2.5 only



LAD Z-score >2.5



LAD Z-score >2.5



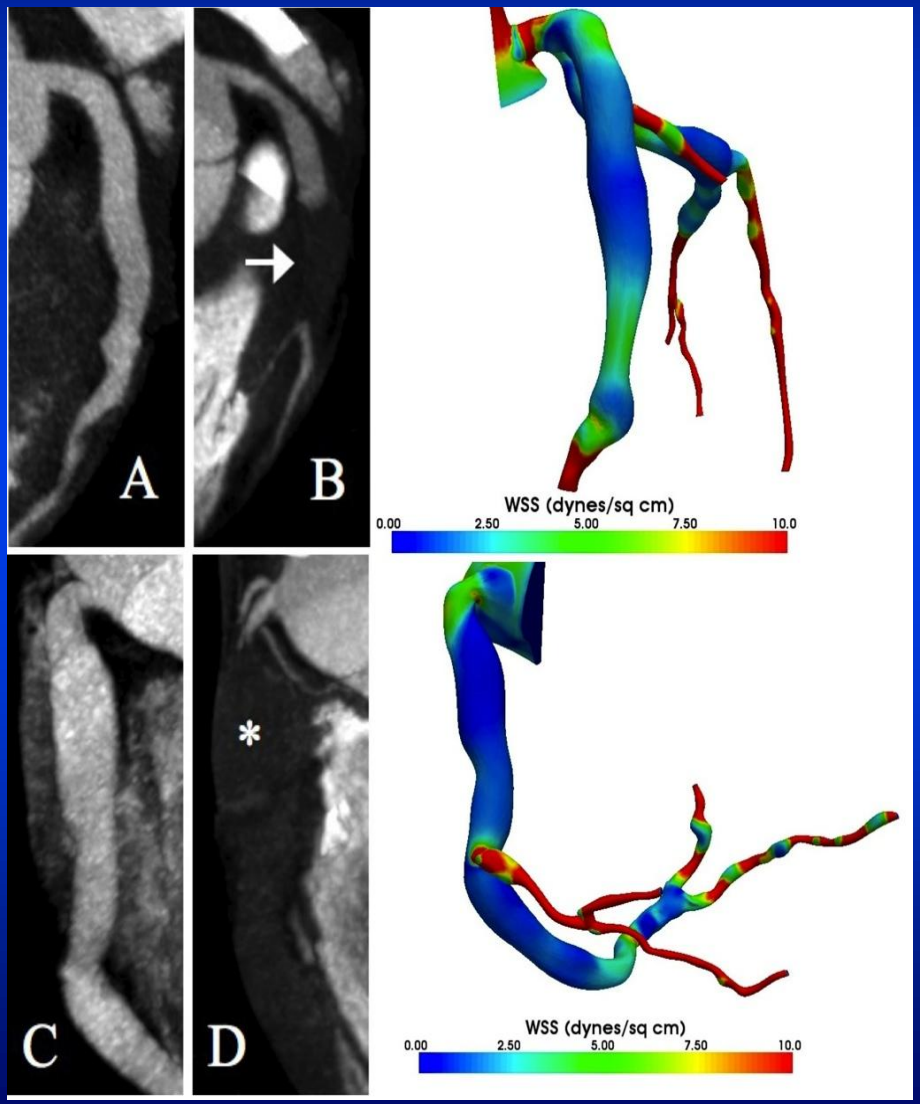
Summary of infliximab effects

- Safe, even in children < 1 year
- No measurable effect on treatment resistance (11%)
- Biologic effect: less inflammation
- Clinical effect:
  - » Fewer days of fever
  - » Larger reduction in LAD Z-score

What is the role of infliximab in KD?

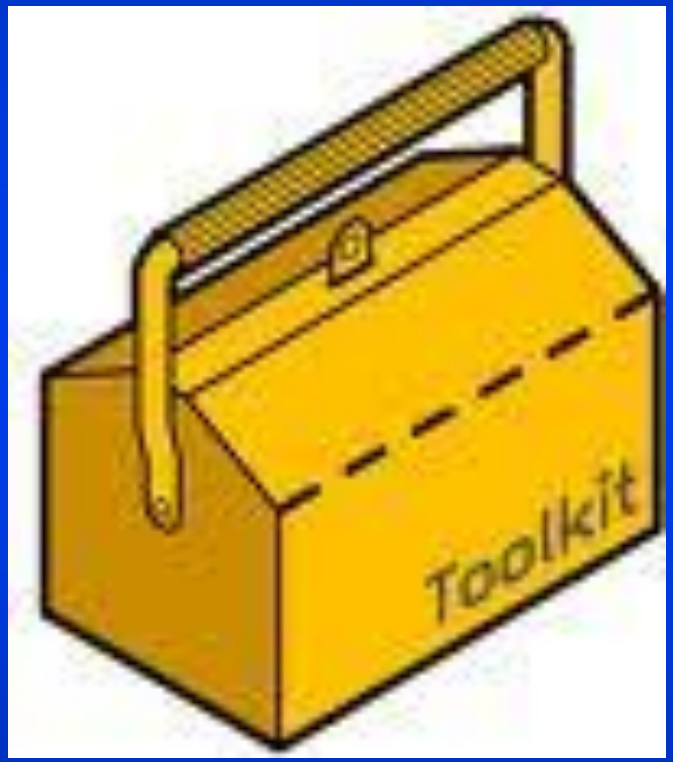
- **Primary therapy:**
  - Safe
  - Data suggest biologic/clinical effect but no reduction in treatment-resistance
- **Rescue therapy for IVIG-resistance:**
  - Safe alternative to 2nd IVIG but efficacy unproven
  - RCT by Yokohama group in progress
- **KD patient with shock or aneurysms**
  - Consider addition of infliximab

Computer simulations predict thrombosis risk



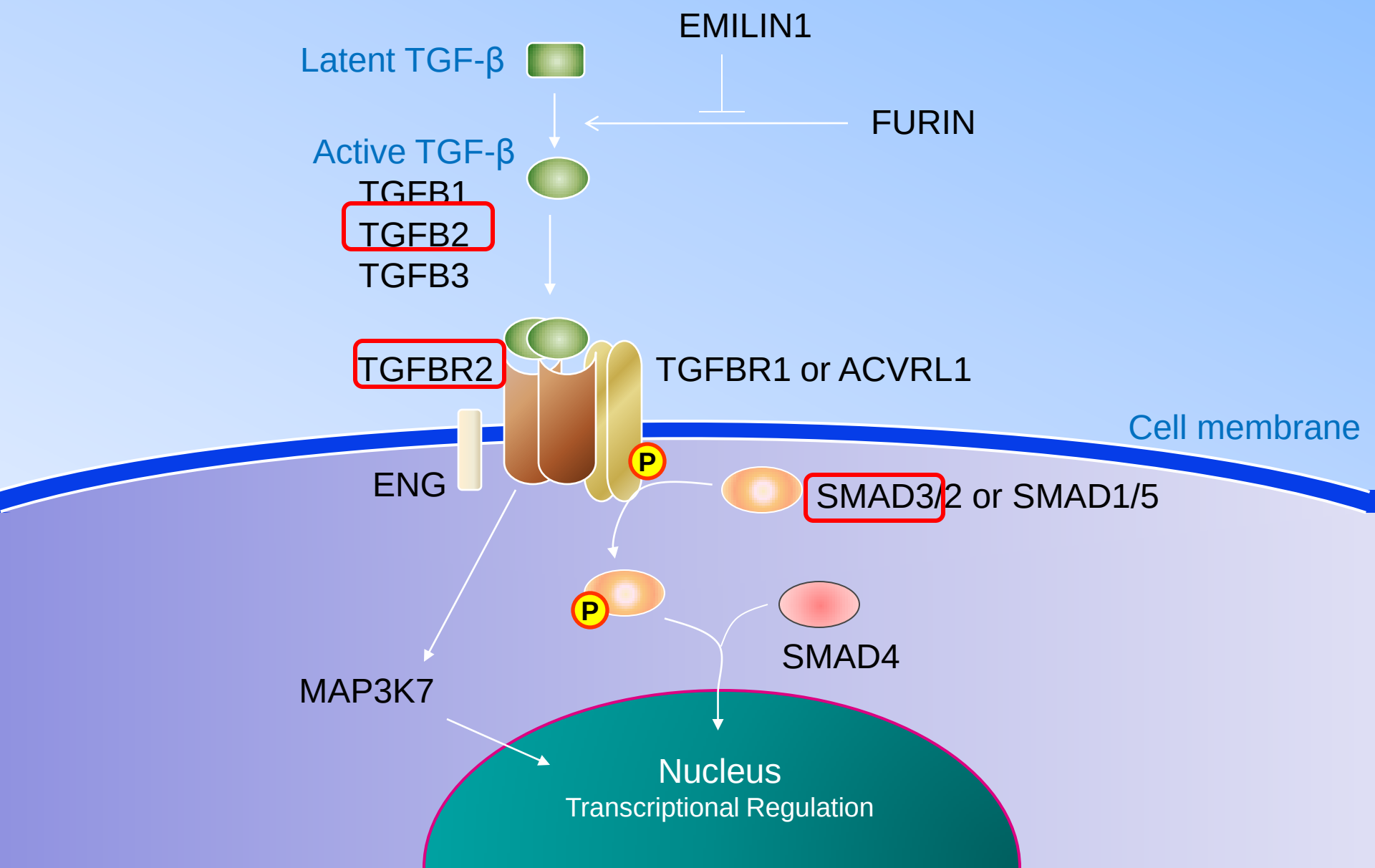
Pre-and post thrombosis CT imaging in patient (A-D), and simulation results showing excellent correlation between wall shear stress predictions in simulation and location of subsequent thromboses (arrow and asterisk) at regions of low wall stress (blue).

Using the genetics tool kit to understand KD aneurysms



- Other aneurysm syndromes associated with TGFβ pathway
- Look for genetic variations in genes in the TGFβ pathway that are more frequently associated with
  KD + aneurysms vs.
  KD - aneurysms

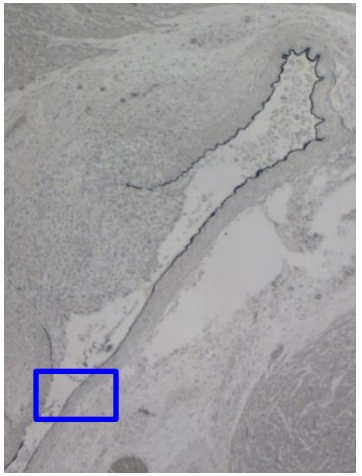
TGFβ pathway



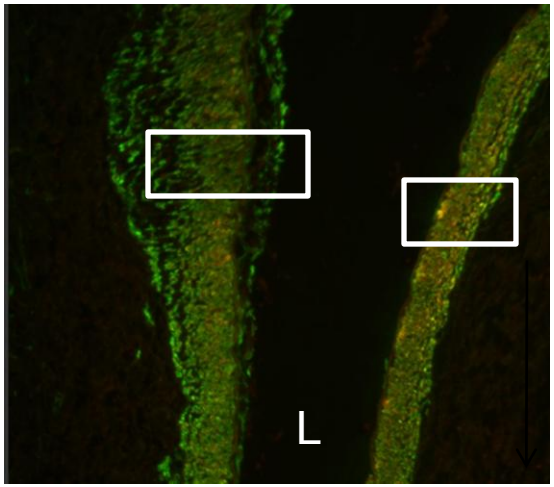
Immunohistochemical studies

- Coronary artery from a 3 mos. old infant with KD who died on Illness Day 12 of myocardial infarction
- Tissues stained with 2 fluorescent antibodies
  - α smooth muscle actin (αSMA) + smoothelin
  - Normal vascular smooth muscle cells stain + for both proteins
  - Myofibroblasts stain only with αSMA

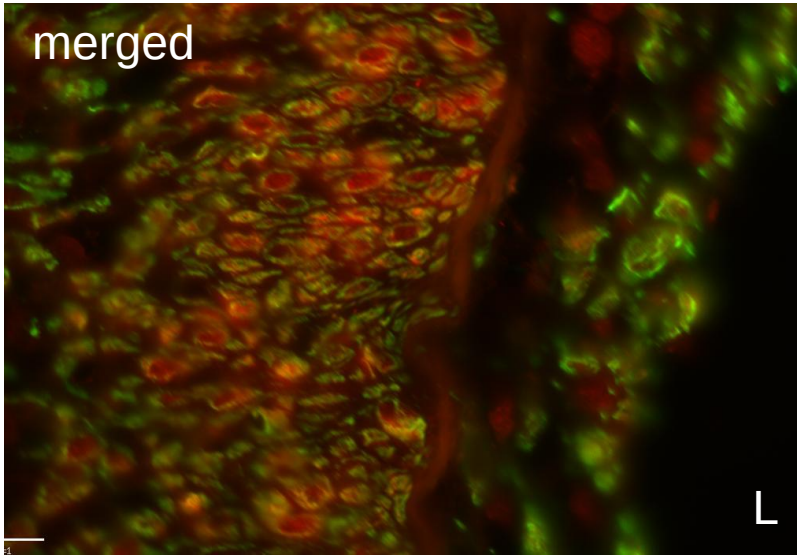
Myofibroblasts in KD arteritis: α-SMA and smoothelin double staining

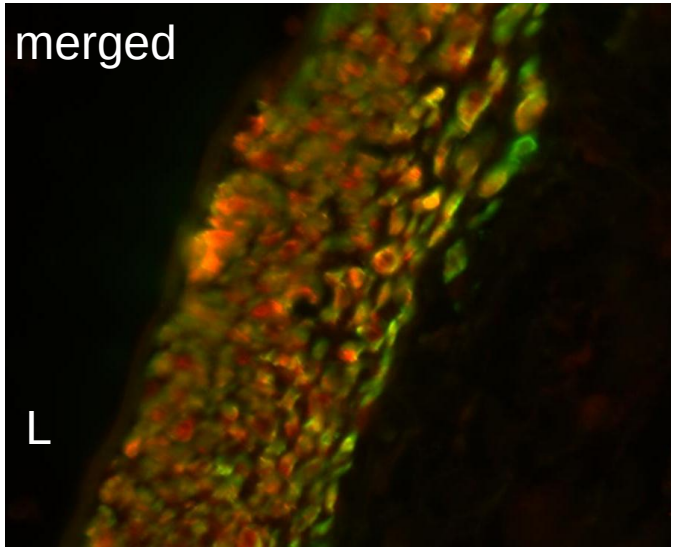


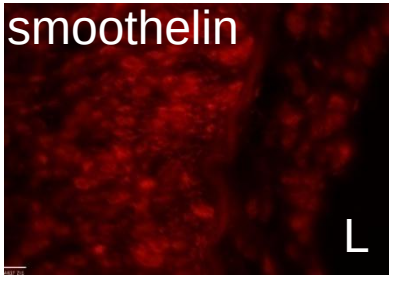
Arteritis side

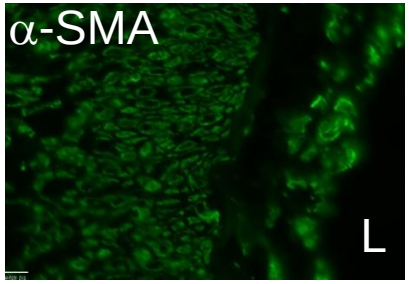


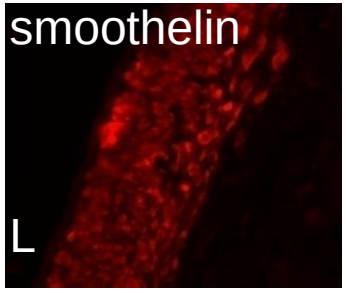
Normal side

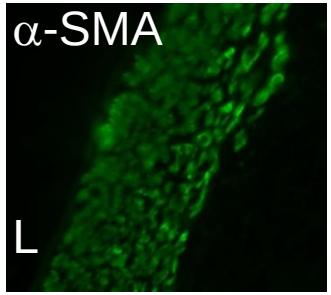






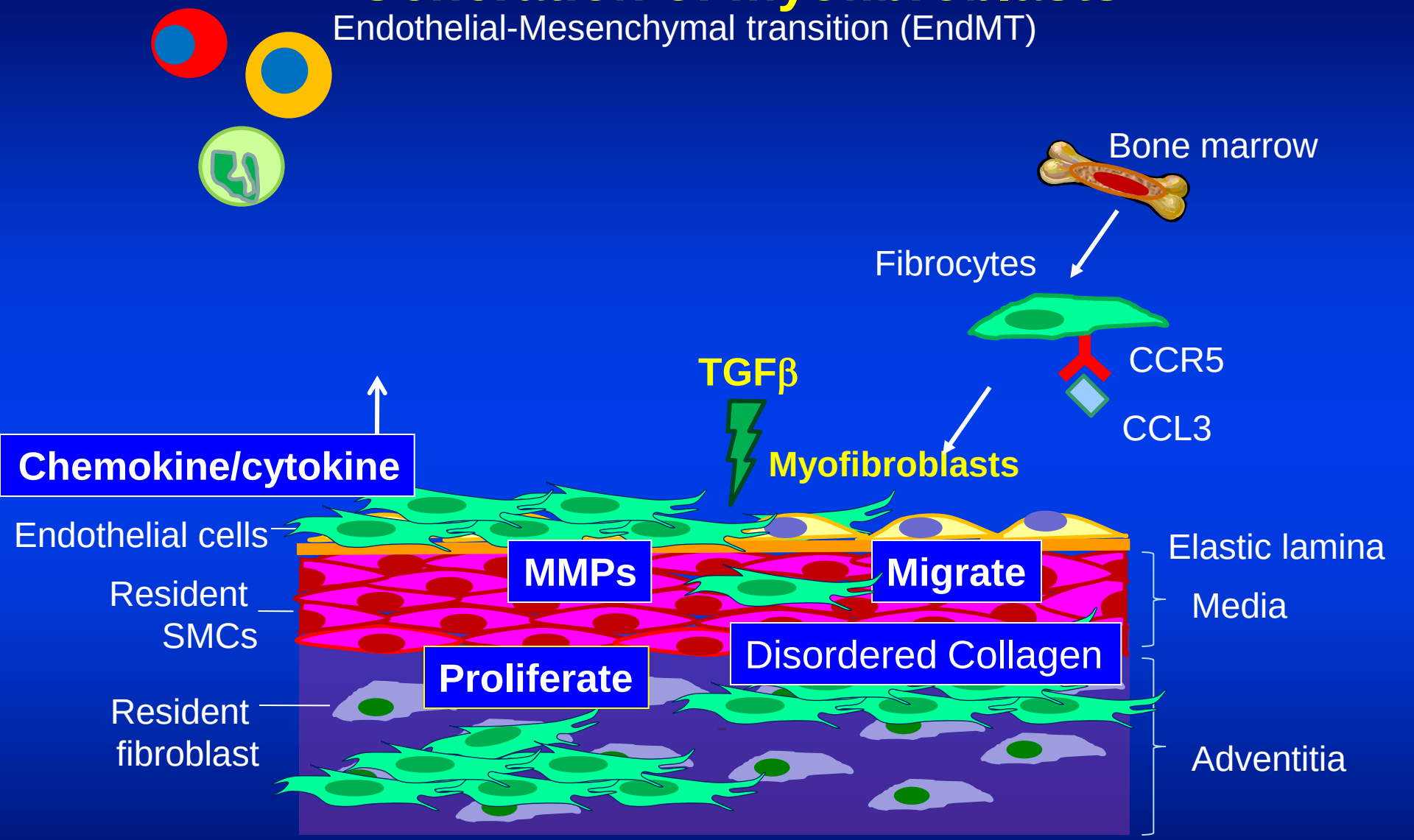






Generation of myofibroblasts

Endothelial-Mesenchymal transition (EndMT)



Current management of coronary artery involvement

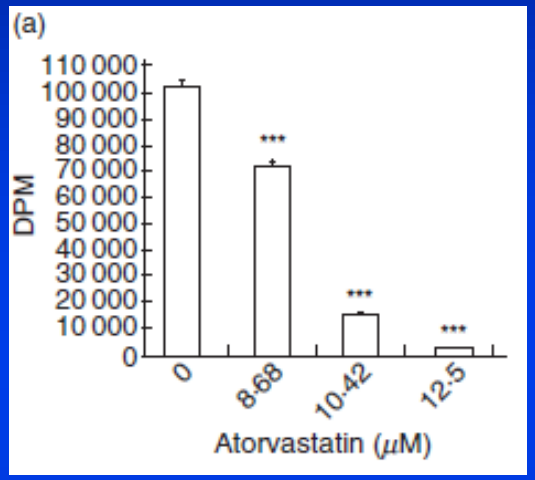
Follow echocardiograms for progression of coronary artery abnormalities

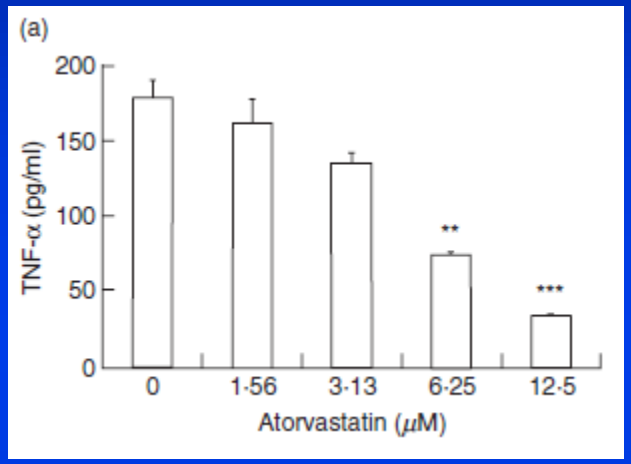
No treatment to **STOP** progression of aneurysms

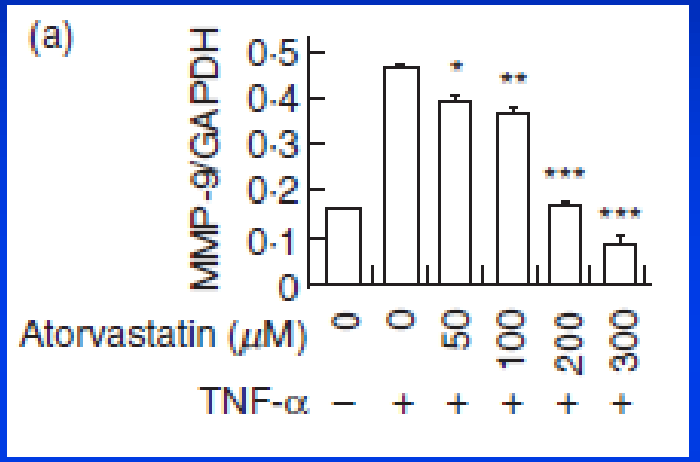
The benefits of statins
(More than just lowering cholesterol)

1. Anti-inflammatory
   - » Inhibit expression of T cell costimulatory molecules
   - » Increase the number and suppressive function of regulatory T cells
2. Antioxidant
3. Prevent vessel damage & promote vessel healing
   - » Reduce epithelial to mesenchymal transition that creates myofibroblasts
   - » Inhibit secretion of MMPs
   - » Increase number of circulating endothelial progenitor cells

KD mouse model & atorvastatin







Dose dependent decrease of T cell prolif (^{3}H incorporation), TNFα, and MMP-9

Blankier, Clin Exp Immuno, 2011

Phase I/IIa trial of atorvastatin for acute KD

Adriana Tremoulet, MD, MAS
Jane C. Burns, MD
University of California, San Diego

Website: Clinicaltrials.gov

Rady Children's Hospital San Diego

KAWASAKI DISEASE RESEARCH CENTER
RADY CHILDREN'S HOSPITAL/UC SAN DIEGO

UNIVERSITY OF CALIFORNIA · SAN DIEGO · LET THERE BE LIGHT

Safety in Children

- FDA-approved for children 8-18 years old with familial hypercholesterolemia
  - » SAFE
  - » Did not impair growth
  - » Did not impair sexual development

Hypothesis

A 6-week course of atorvastatin

will promote healing of early coronary artery abnormalities

in children with Kawasaki disease

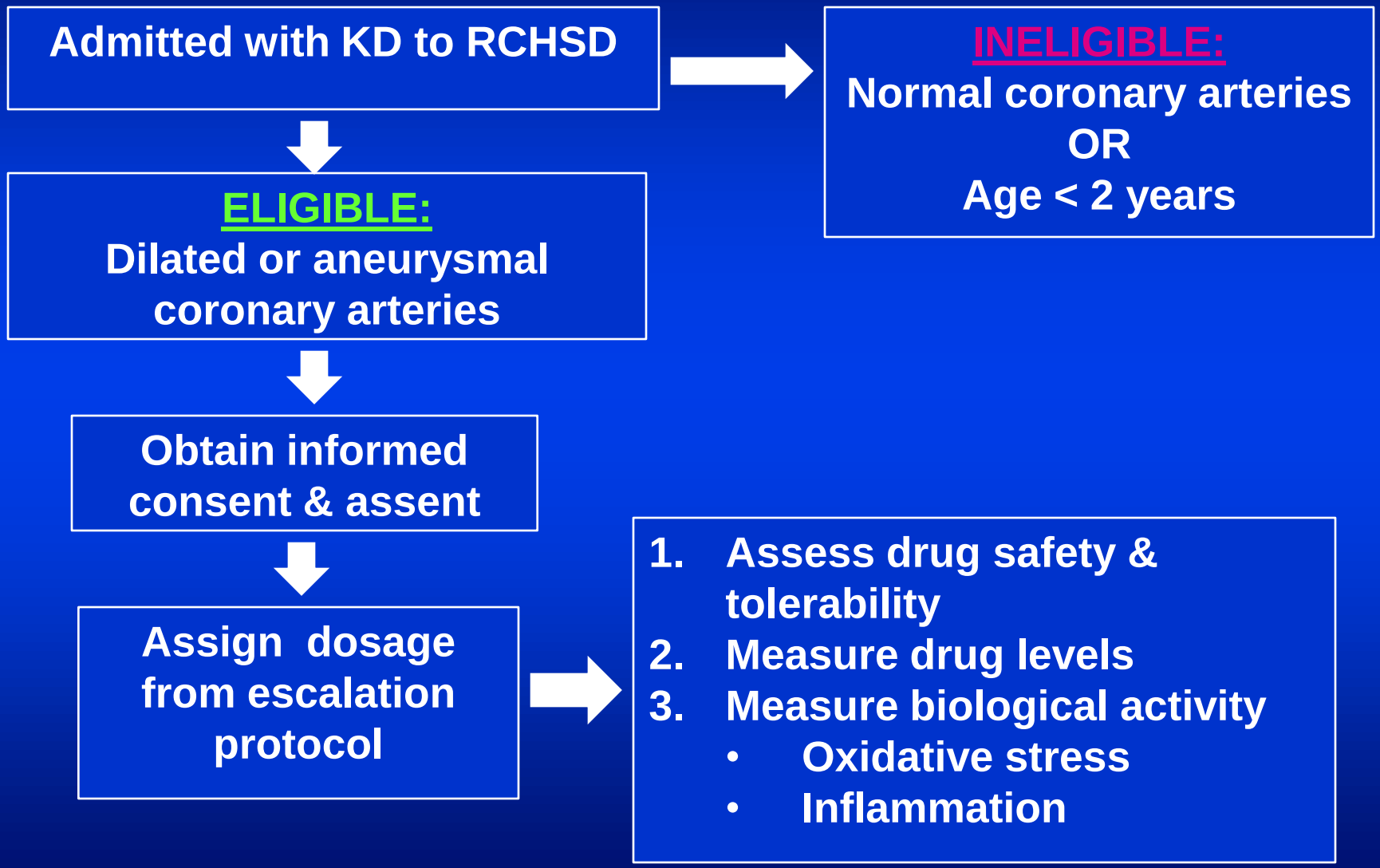
Specific Aims

1. **Test safety of escalating doses of atorvastatin in infants and children with KD and coronary artery abnormalities**

2. **Pharmacokinetics of atorvastatin in patients with KD**

3. **Exploratory aim: Test whether atorvastatin will reduce inflammation and oxidative stress, induce T-cell regulation, and improve echocardiographic outcome compared to matched controls.**

KD atorvastatin study design



Atorvastatin study dosing regimen

Atorvastatin dose escalation scheme		
Dose cohort	Daily dose	No. of subjects
1	0.125 mg/kg/day	3-6
2	0.25 mg/kg/day	3-6
3	0.5 mg/kg/day	3-6
4	0.75 mg/kg/day	3-6
TOTAL		12-24

Safety monitoring

- Baseline fasting lipid panel, liver enzymes, CPK, ESR, CRP, WBC
- Repeat laboratory testing at 2 and 6 weeks
  - » Adverse event and dose-limiting toxicity defined for each laboratory value
  - » Stopping rules defined

Atorvastatin trial to date

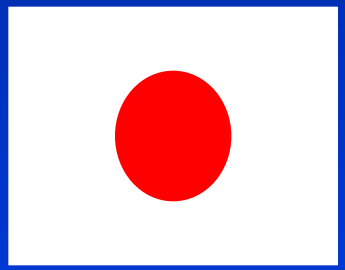
- Added second site: University of Colorado, Denver, Peini Jon, PI

- Enrolled 5 patients: 4 in the lowest dosing cohort, 1pt in 2nd dosing cohort
- No serious adverse events
- DSMB review of data after completion of each dosing cohort

Kawasaki disease: A climate connection?

US Team

Dan Cayan
Emelia Bainto
Jane C. Burns
Marian Melish
Ian Lipkin



Japanese Team

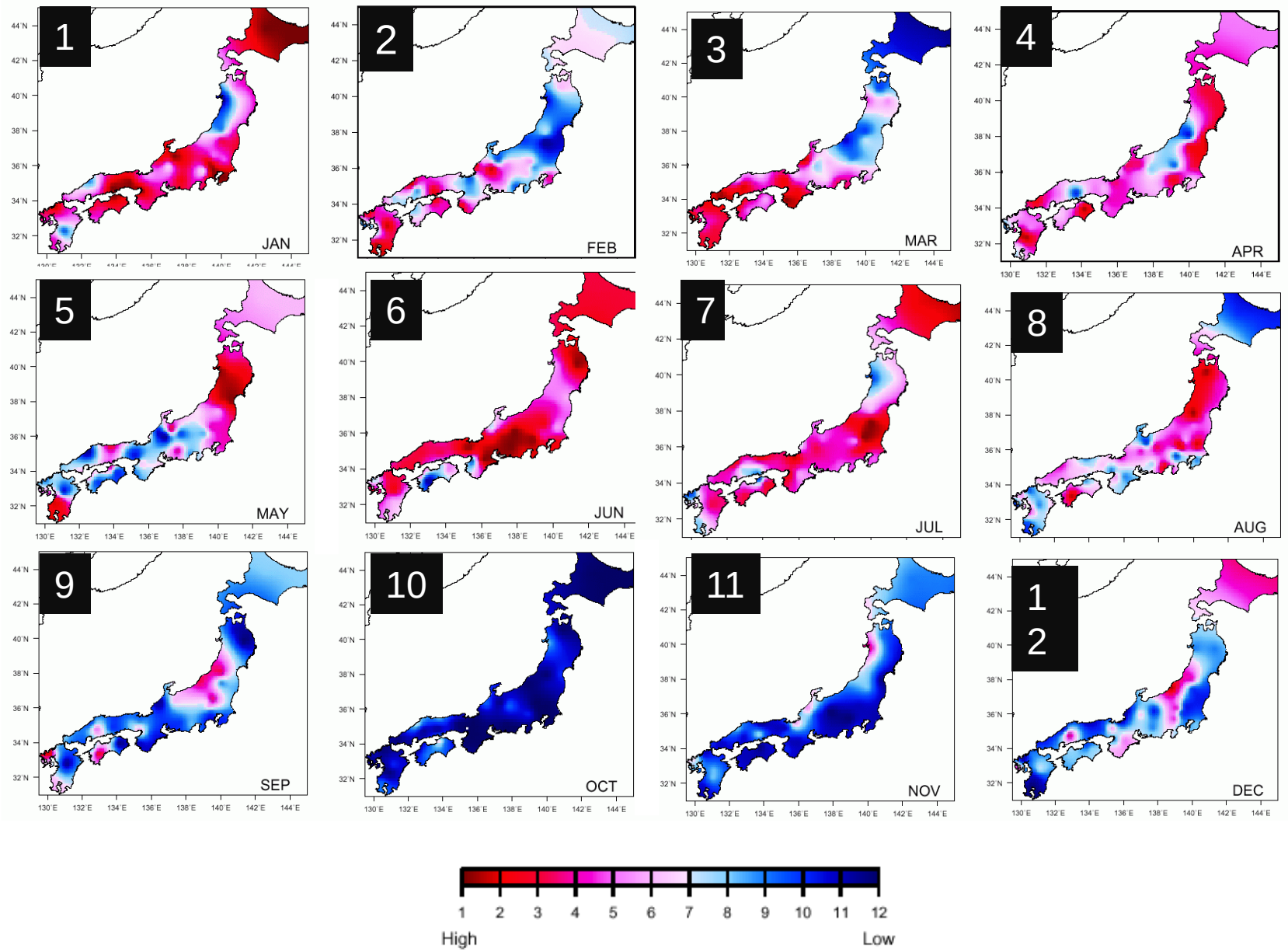
Hiroshi Yanagawa
Yosikazu Nakamura
Ritei Uehara
Mayumi Yashiro
Tomisaku Kawasaki

Catalan Team

Xavier Rodo
Joan Ballester
Jordi Anton

Methods: Seasonality for Japan

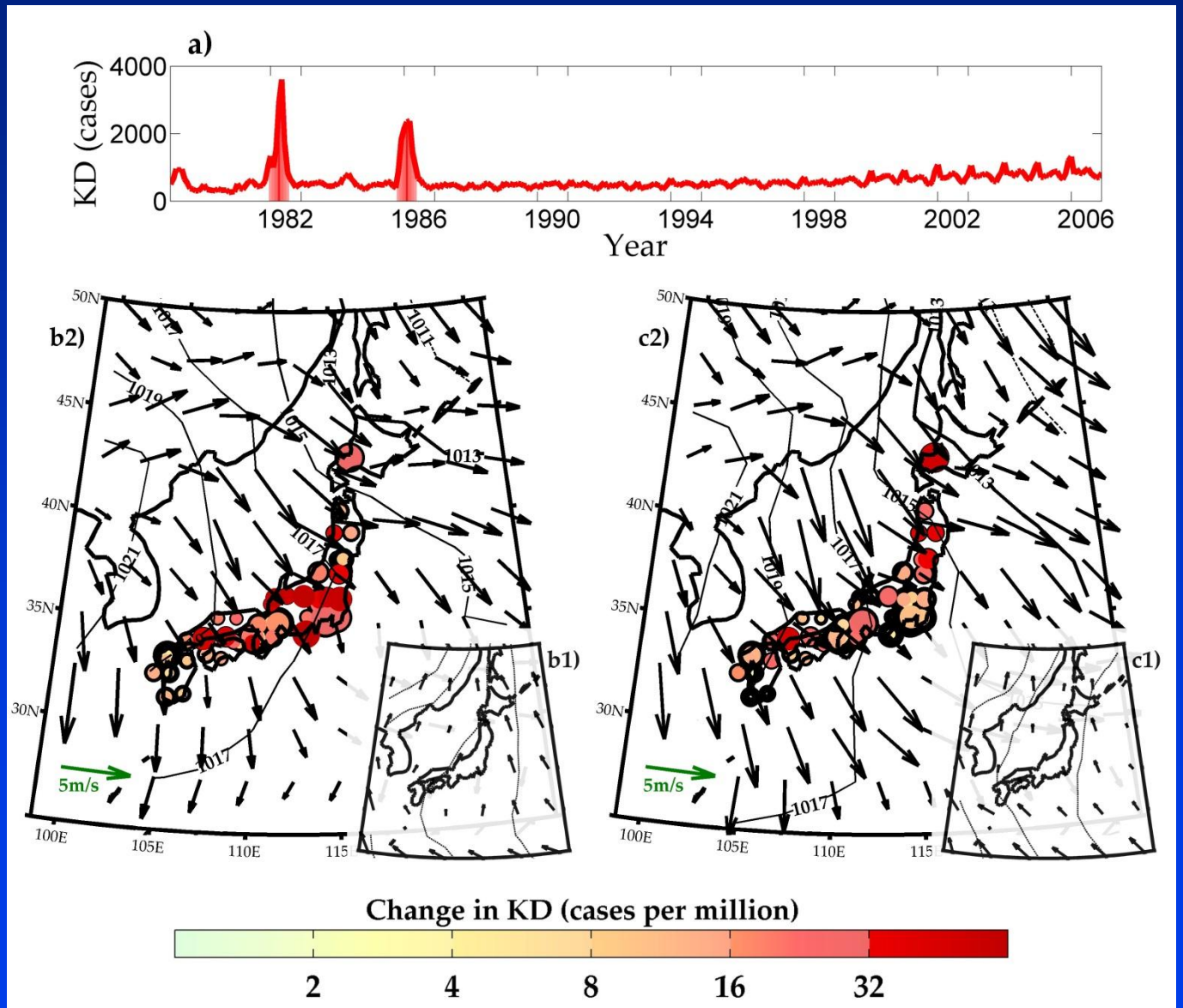
- **135,027 KD cases from 1979-1998 (19 yrs)**
  - » Determined average incidence (# cases/day) for each month and each prefecture
  - » Ranked each month for each prefecture on a 1-12 scale, red=highest, blue=lowest

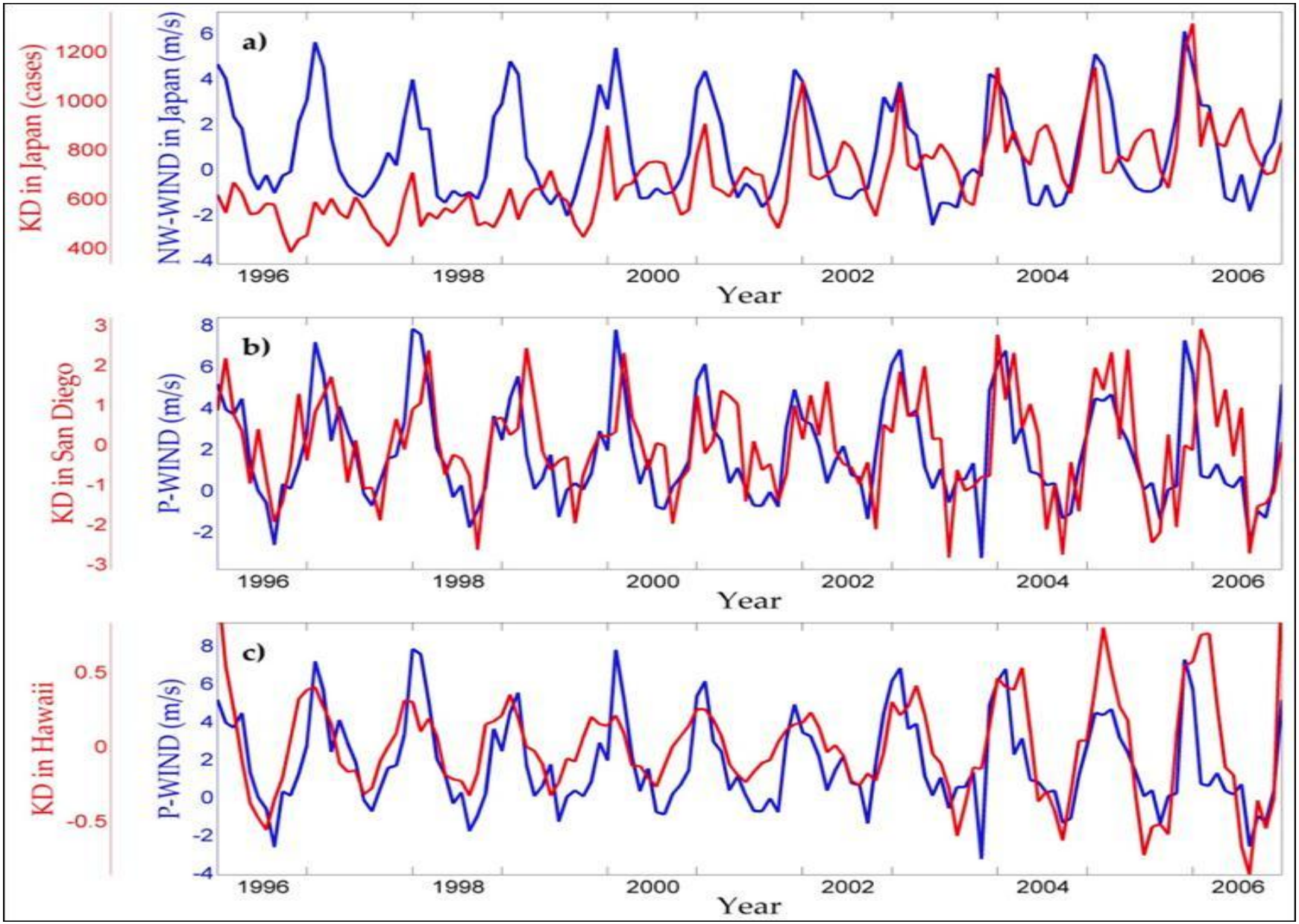

1
JAN
2
FEB
3
MAR
4
APR
5
MAY
6
JUN
7
JUL
8
AUG
9
SEP
10
OCT
11
NOV
12
DEC
1 2 3 4 5 6 7 8 9 10 11 12
High
Low

Hypothesis

- Climate-related factors trigger KD
  - A regional-scale climate pattern precedes the onset of a KD cluster

Major Epidemics of KD in Japan





KD and surface winds in Japan (a), San Diego (b) and Hawaii (c).

Barcelona Hypotheses

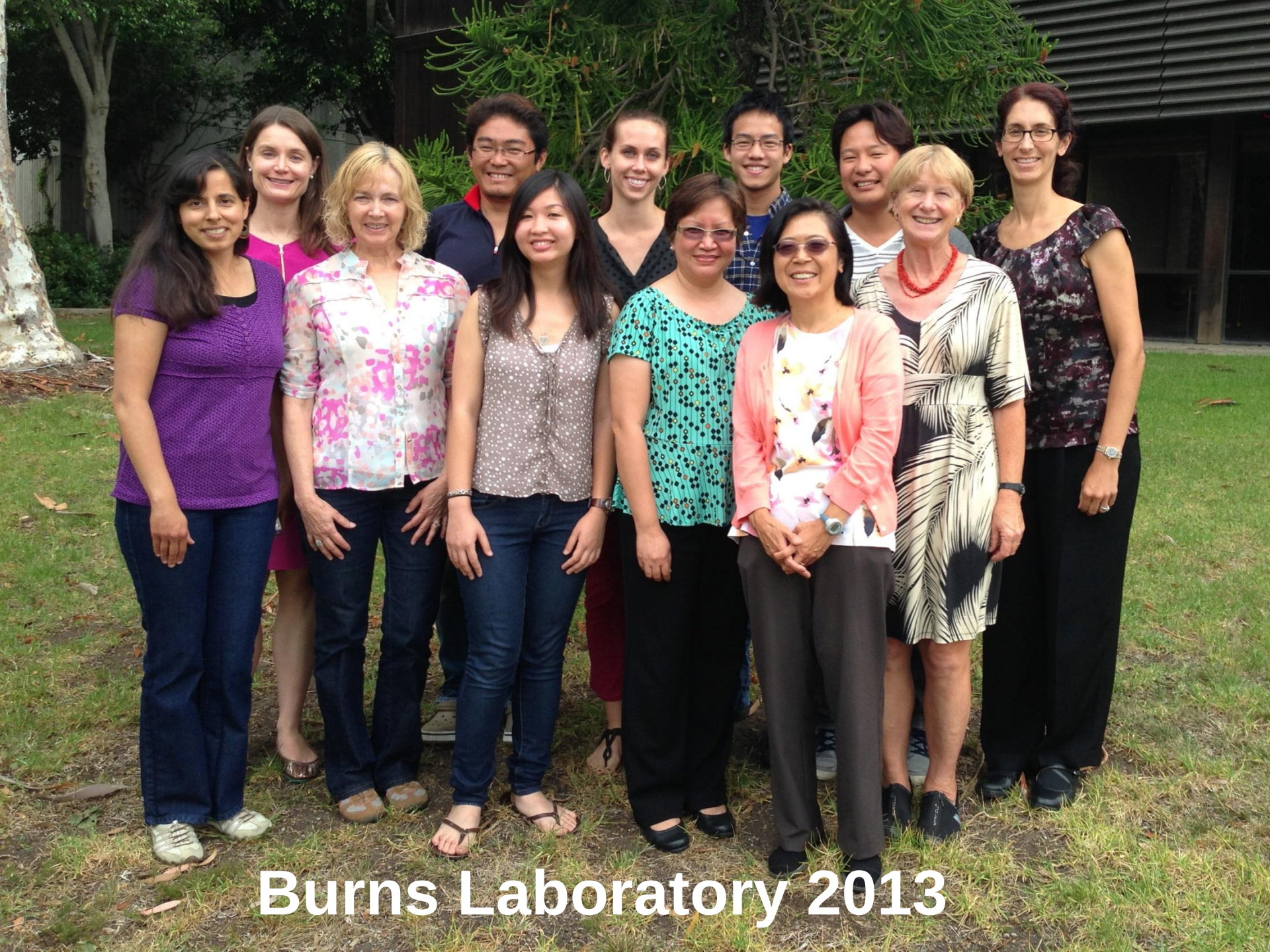
The Barcelona meeting hosted by IC3 in September 2010 was attended by representatives from Japan, US and Western Europe

Hypothesis #1:

- Tropospheric winds carry an agent that when inhaled by genetically susceptible infants and children causes KD

Hypothesis #2:

- The KD agent is transmitted through aerosolized dust particles that originate from somewhere in Central Asia


Burns Laboratory 2013