Update on the Immunology of Acute Rheumatic Fever

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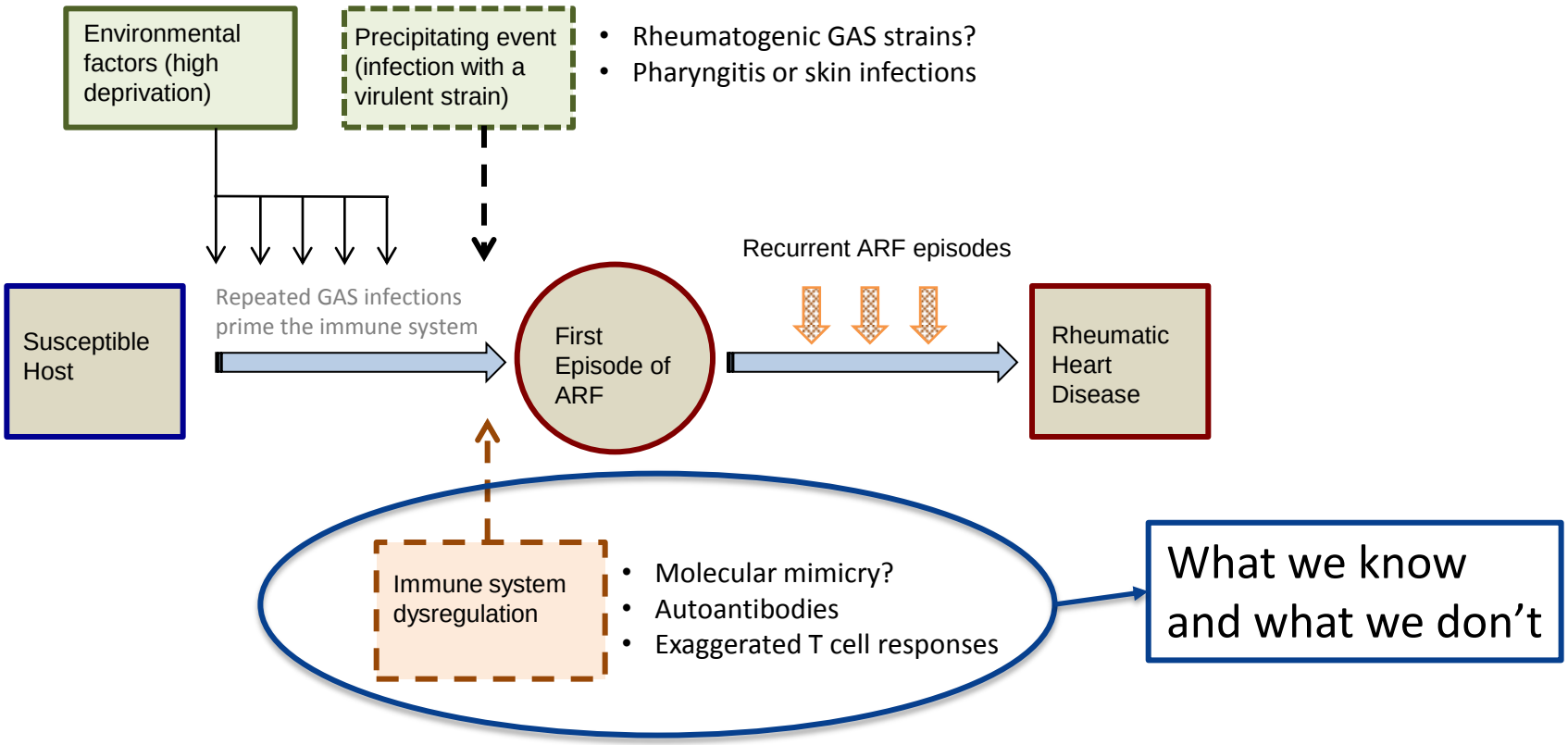
Outline

- Current model of ARF pathogenesis
- Two prevailing theories regarding development of autoimmunity in ARF
- New research approaches to study ARF immunology

ARF Pathogenesis



Adapted from Carapetis et al., Lancet, 2005

RF is an Immune Mediated Disease

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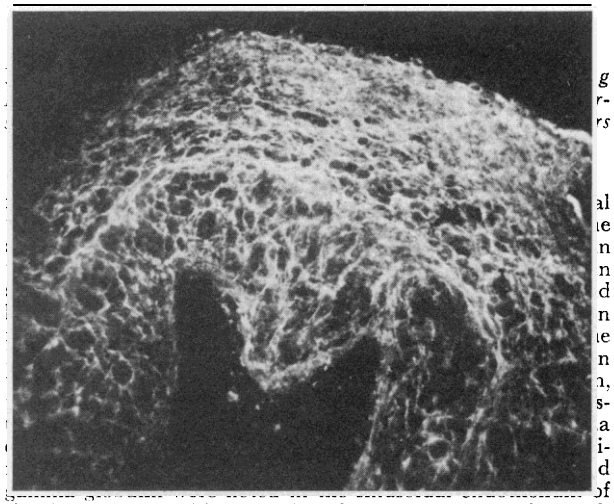
Antibody deposit on mitral valves (Kaplan et al 1964)



the liver. It was of interest that the external layer of smooth muscle of the small intestine and overlying visceral peritoneum exhibited deposits of gamma globulin. Skeletal muscle of psoas muscle, diaphragm and femoral adductors showed occasional foci of gamma globulin in sarcolemma and endo-

CD4+ T cells infiltrate mitral valve endothelium (Quinn et al 2001)

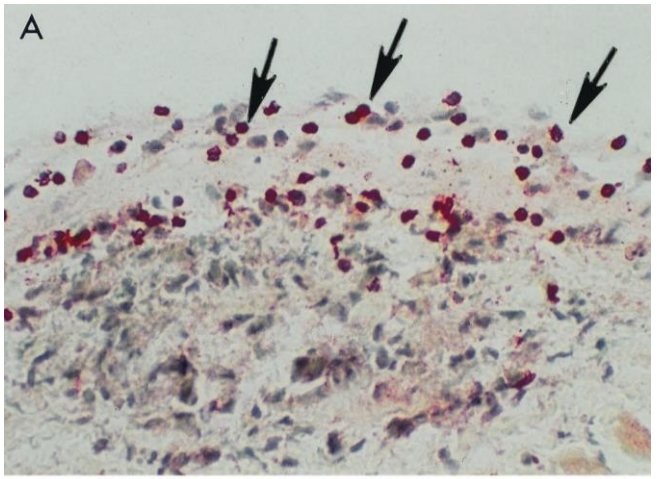
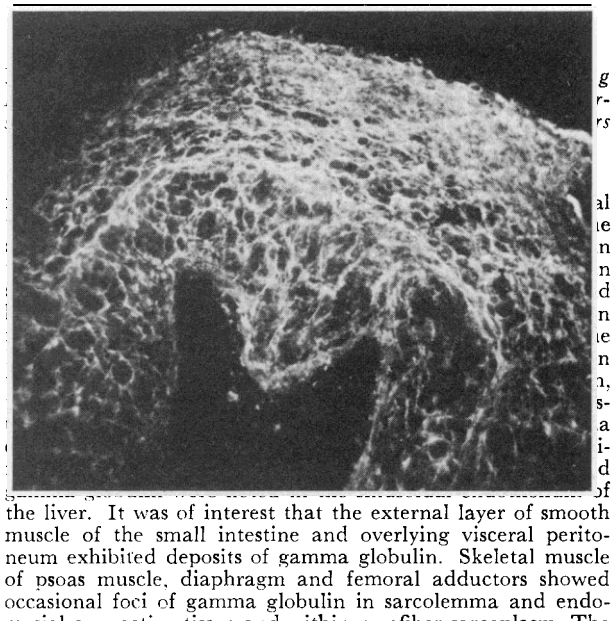


FIG. 5. Human rheumatic heart valve section reacted with anti-$CD4^+$ antibody shown for comparison with the rat valve sections. The human rheumatic valve section (A) illustrates the infiltration of $CD4^+$ lymphocytes (stained with fast red) through the endothelium into the valve and the presence of a necrotic Aschoff body in the valve tissue.

How are Autoantibodies generated?

Antibody deposit on mitral valves (Kaplan et al 1964)



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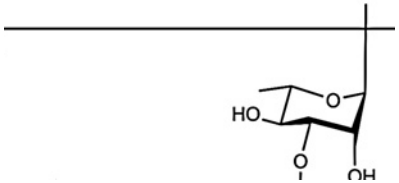
1. Mimicry (Cunningham Lab)

M protein

Group A Carbohydrate



Mimicry with α-helical proteins

- Myosin*
- laminin
- keratin

(*Intracellular)

Mimicry with glycosylated proteins or carbohydrate epitopes

- Defined for chorea but not carditis

Reviewed in Carapetis et al., NRDP, 2016

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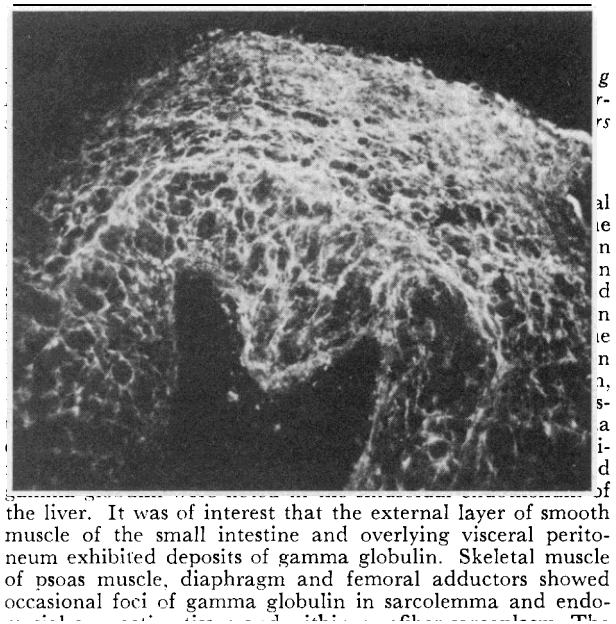

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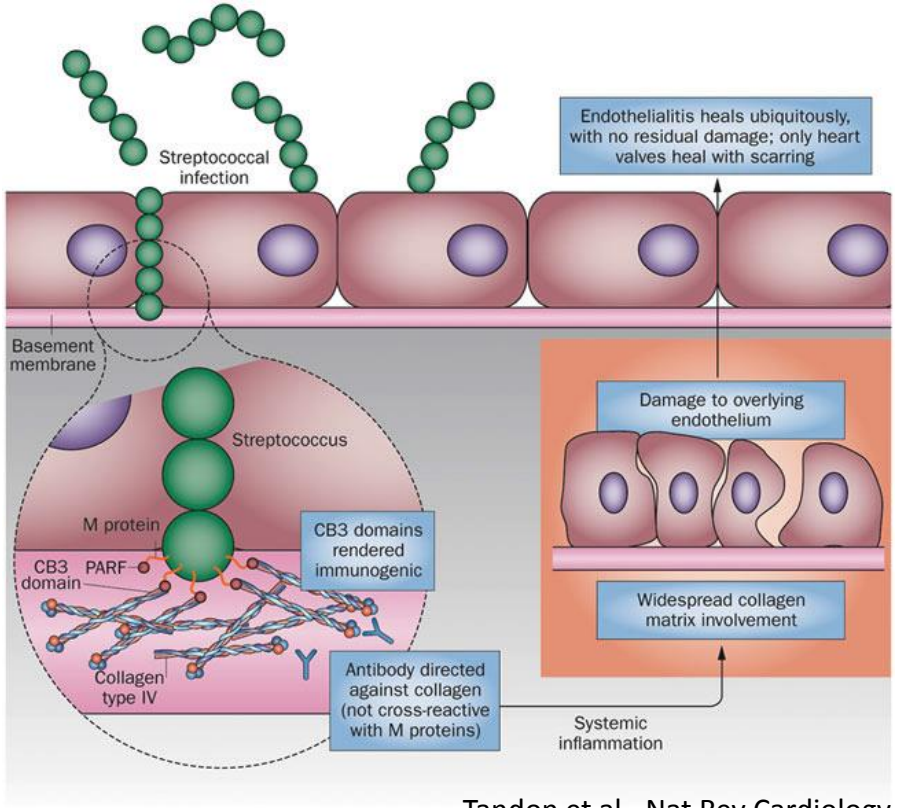
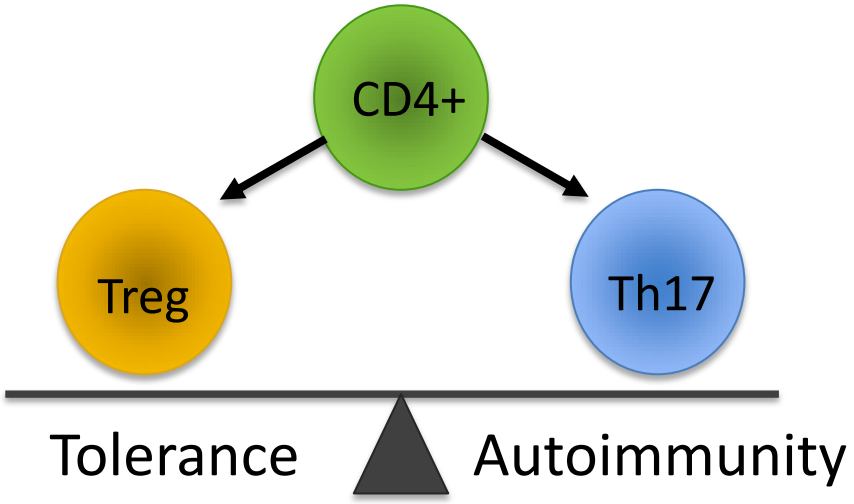
2. Collagen



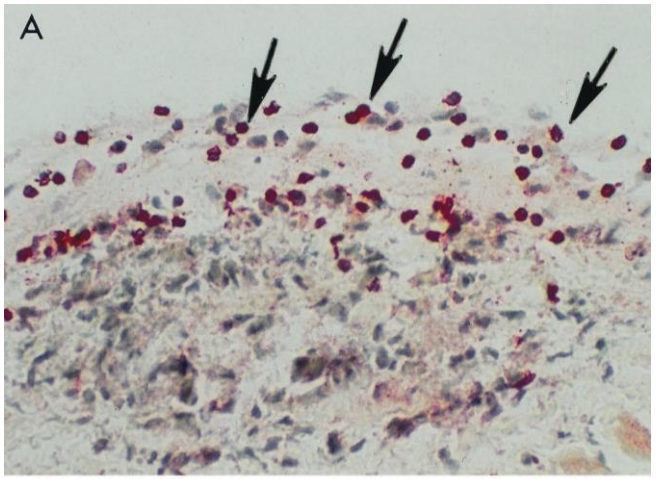
Tandon et al., Nat Rev Cardiology, 2013

How do T-cells drive Autoimmunity?



- Th17 cells associated with other autoimmune diseases
  - Psoriasis, rheumatoid arthritis, Crohn's disease
- Elevated Th17 in RHD (Bas et al., 2014)

CD4+ T cells infiltrate mitral valve endothelium (Quinn et al 2001)



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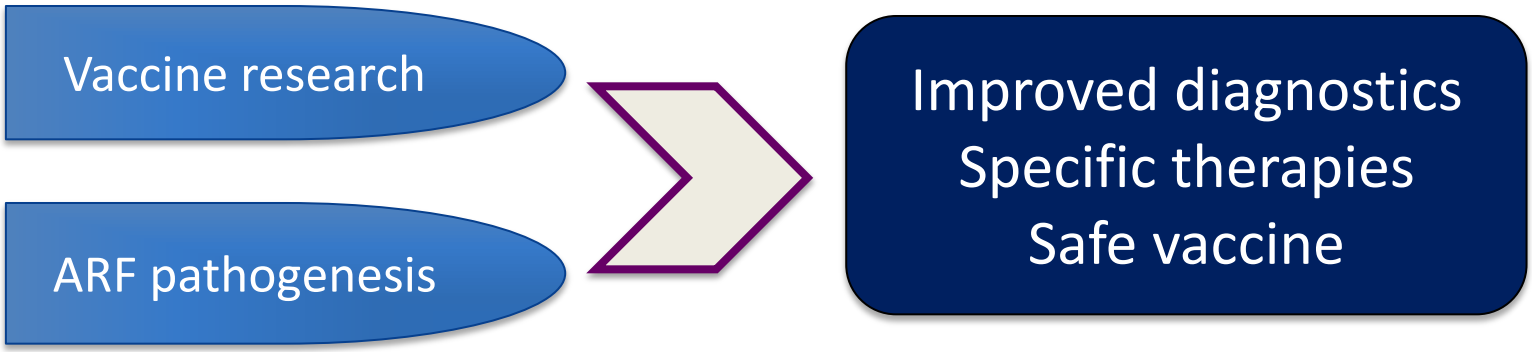
Pressing Research Need

- Pathogenesis remains poorly understood
  - Lack of biomarkers and specific diagnostics for ARF
  - No specific therapies for ARF
  - No effective vaccines for GAS (Safety hurdle)



New Technologies enable Immune Profiling

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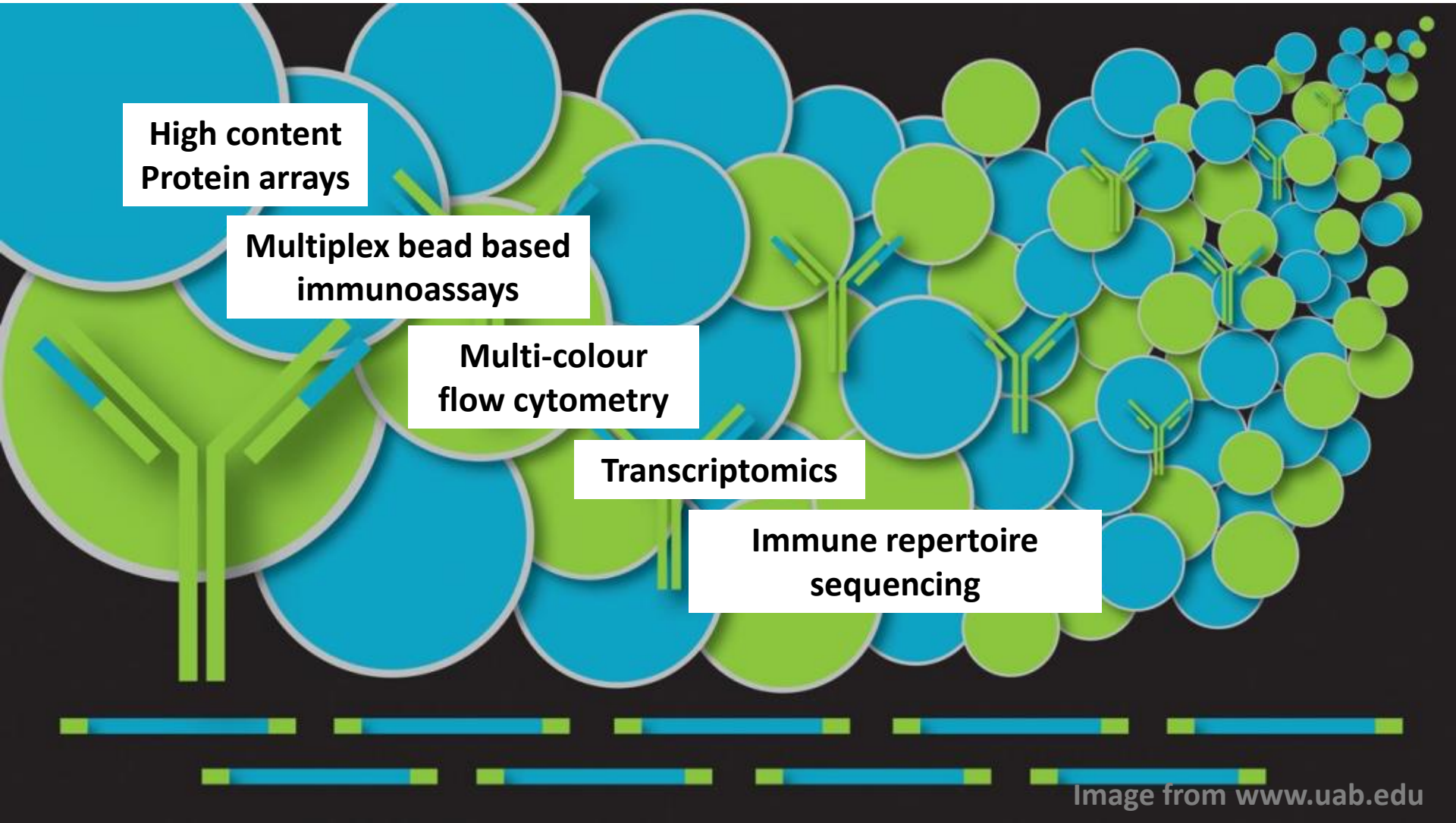


Image from www.uab.edu

Clinical samples

1. Pilot cohort

Waikato DHB (n=8)

Drs Polly Atatoa Carr, Anita Bell (2012-2015)

Starship (n=8)

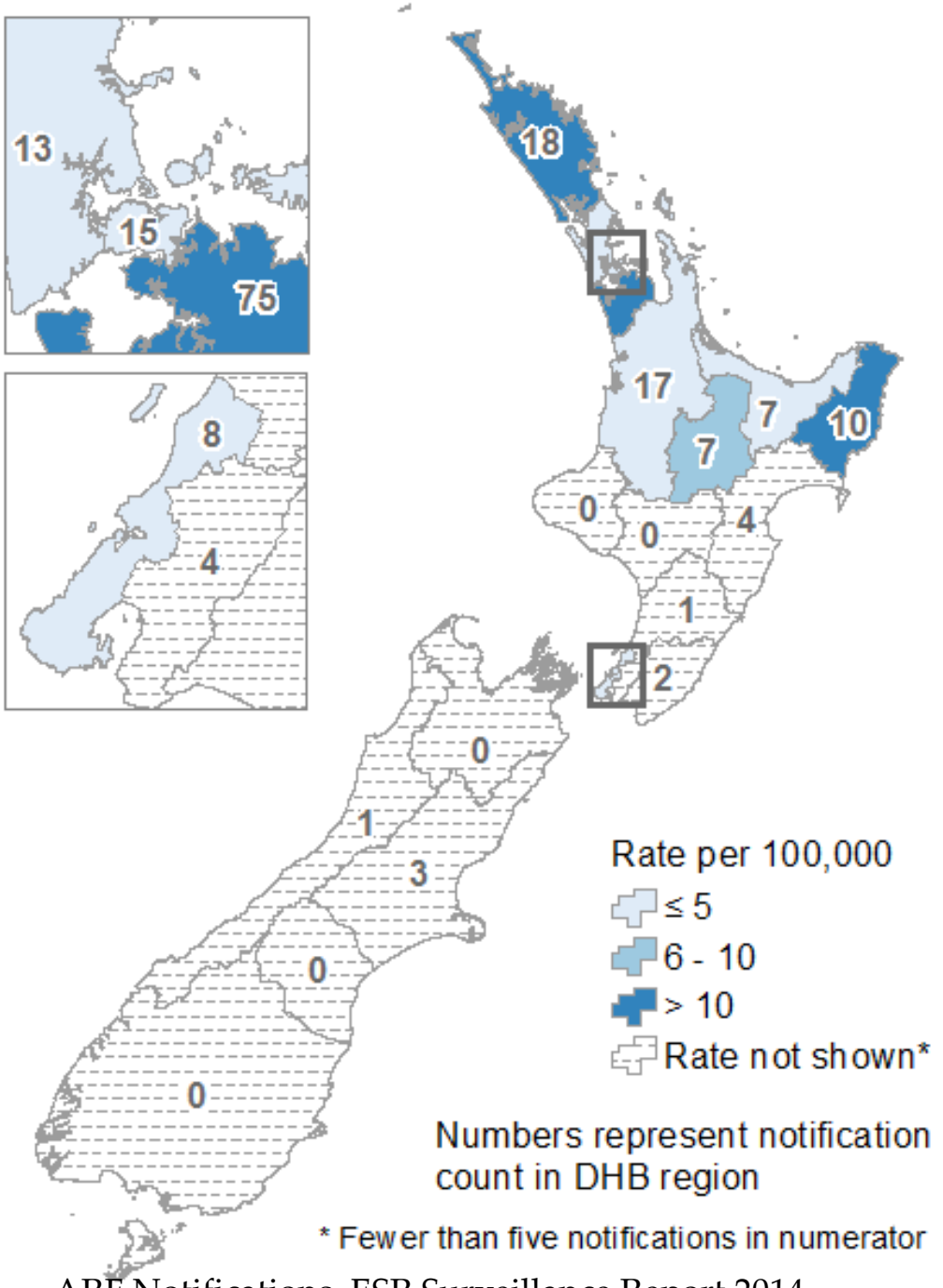
Prof Ed Mitchell (2005)

2. RF Risk factor study

Prof Michael Baker (Otago)

Prof Dinny Lennon (Auck)

- Northland
- Counties-Manukau
- Auckland
- Waitakere
- Waikato
- Hutt-Capital Coast



ARF Notifications, ESR Surveillance Report 2014

ARF Immunology Research in Auckland

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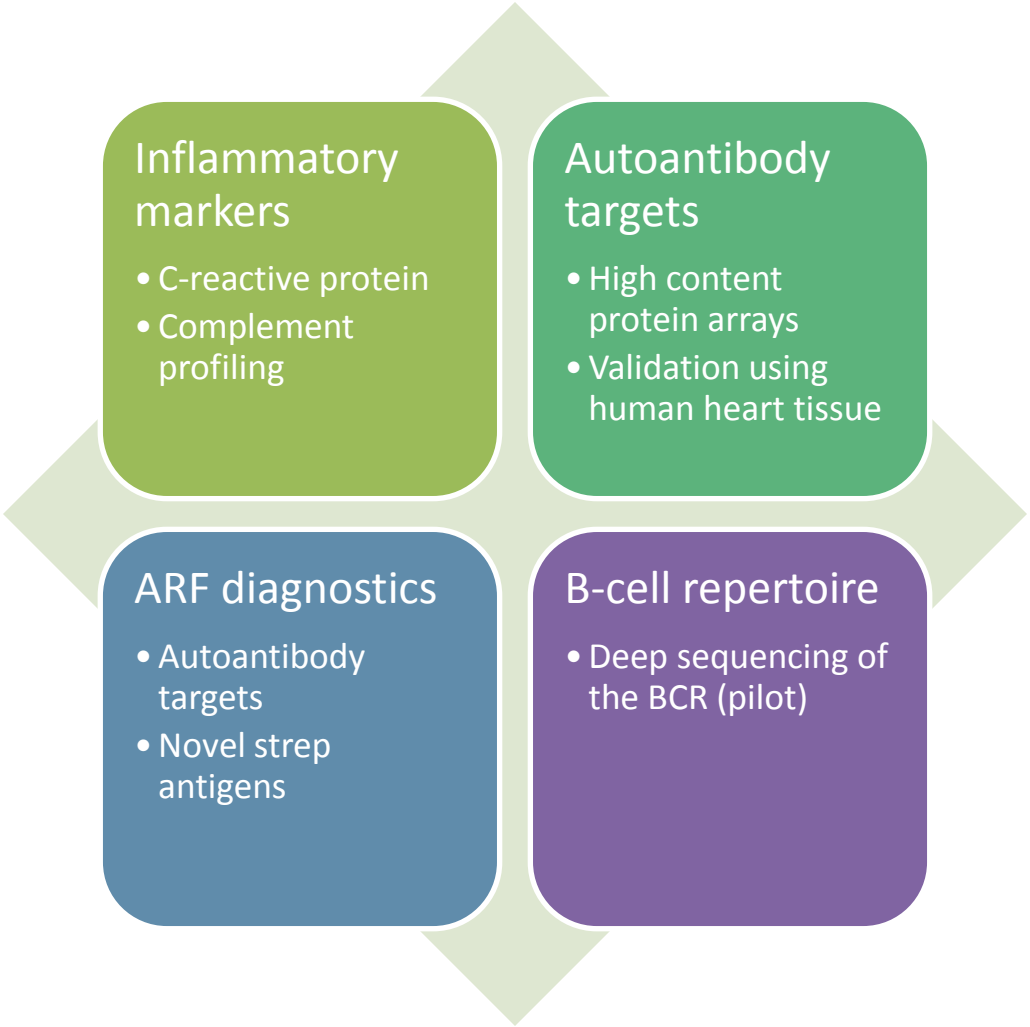
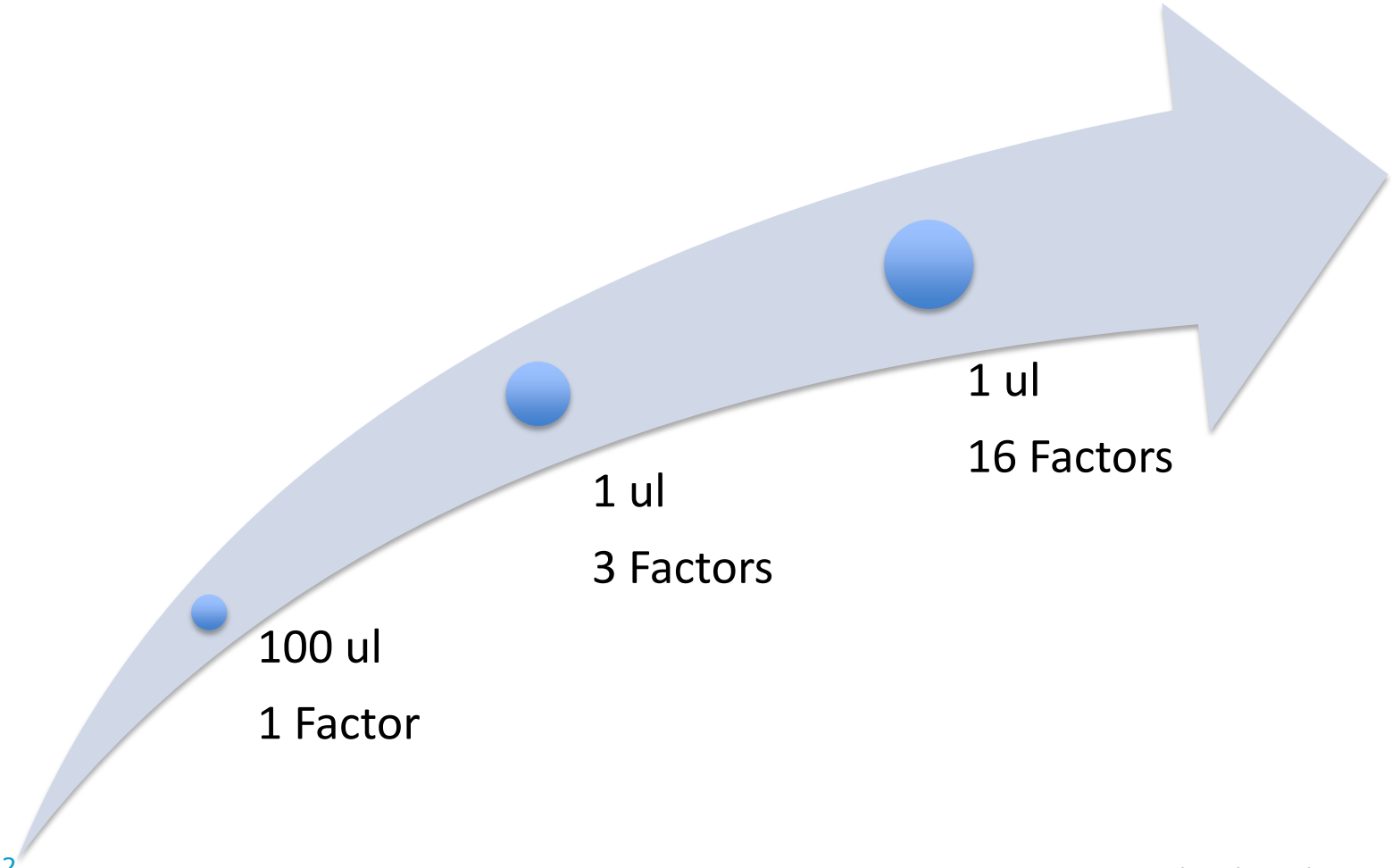


Measuring CRP and Complement



High Content Protein Arrays (I)

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- Pilot study (ProtoArrays, Life Tech)
  - ARF (n=4), Phar (n=3), HC (n=3)

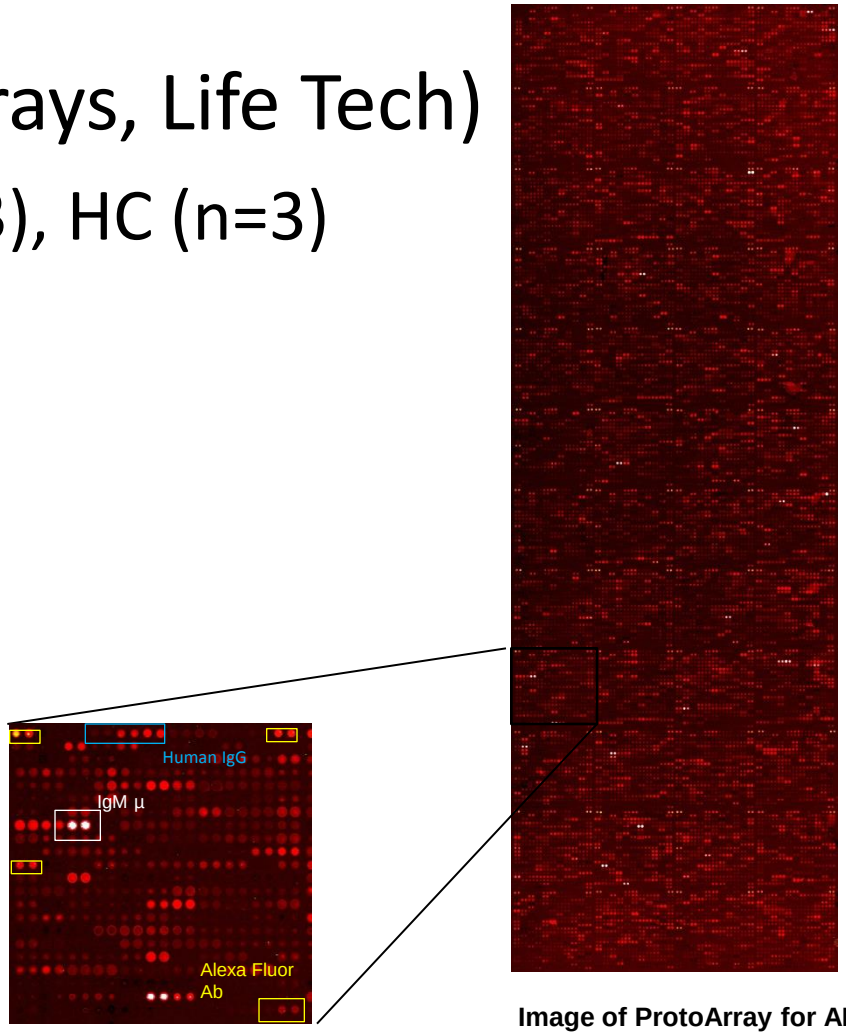

Image of ProtoArray for ARF patient A1

A Contemporary Disease Model for ARF

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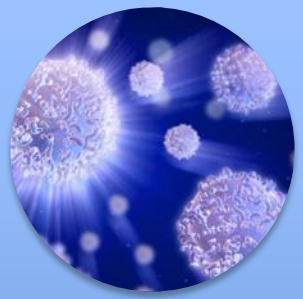
Systems Biology

Antibody repertoire



Cellular Immunology

Transcriptome

Signaling Molecules

Summary

- ARF pathogenesis is poorly understood
- New technologies for immune profiling have great potential to improve disease models
- Collaborative efforts will enable a systems biology approach

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RF Risk Factors Study
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Debbie Williamson

WEHI
Willy John Martin
Ian Wicks

Telethon Kids
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Meru Sheel

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