Vaccinations in rheumatology patients at home and abroad

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TRI
partnering for better health

The University Of Queensland
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Diamantina Institute for Cancer, Immunology and Metabolic Medicine

Disclosure

- Director of Dendright
- Dendright Pty Ltd in R&D collaboration with Janssen Biotech, Inc to develop and commercialise tolerizing immunotherapy for the treatment of rheumatoid arthritis

Case

- Mrs DM, 77 y.o, caucasian female:
  - Seropositive deforming RA with functional limitations:
    - Methotrexate 15 mg/week (1997)
    - FA 5 mg/week, 6/7.
    - Prednisolone 5 mg/day
    - Paracetamol prn
  - Background h/o
    - Osteoporosis.
    - IHD
    - Asthma
    - Hypothyroidism.
  - Clinically stable on current regimen.

GP:

- Her husband has shingles.
- Should he vaccinate Mrs. DM with VZV?

Your choice?

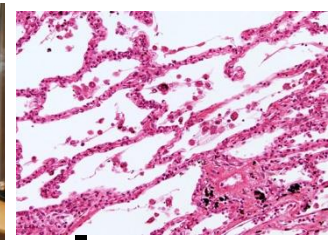
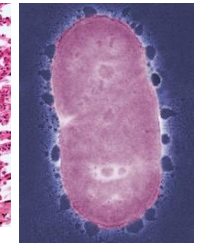
- Vaccinate
- Should not vaccinate
- Depends on antibody status

Immunity and Immunosuppression in Rheumatic Diseases

- Genetic predisposition to abnormal infection response
- In RA, more frequent soft tissue, skin, respiratory infections
  - Lymphopenia predicts risk
- In other AIRD, respiratory infections
- SLE>RA
- Additional immune suppression by treatment: DMARDs, corticosteroids, biologics
  - TNFi: TB, non-TB M, PCP, histoplasmosis, pneumococcus mortality
- Vaccination to prevent common infections and their consequences
  - Pneumococcal vaccine
  - Influenza
  - Tetanus toxoid
  - Live vaccines: VZV, yellow fever (MMR, BCG)

Pathogenesis of Rheumatoid Arthritis

Environmental
(e.g. Smoking, Infections, silica)

Increased effector memory cells
Increased regulation
Anergy: reduced recall/memory response
Increased cross reactivity
Good B cell responses unless depleted

HLA-DRB1*0401, 0404, 0408, 1001 0405, 0101

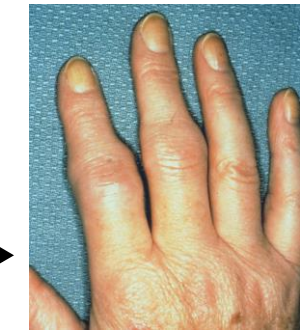
Aged immune system

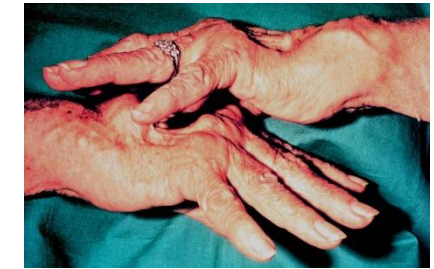
Genetic risk
HLA "shared epitope"
Genes affecting Ag modification, effector and regulatory T cell function, innate immunity

Stress!!

Inflammatory cell death

Antibodies against modified self (ACPA)





Risk of VZV in rheumatic disease

- 98% seropositive VZV
  - Primary infection
  - Live attenuated VZV vaccine introduced 1995, 85% seroconversion, may get infection response
  - At risk Zoster: primary or vaccine-associated infection
  - Protective Zoster: CMI (ELISPOT test) not antibodies
  - If lose AB, at risk of new infection (exposed to chicken pox or Zoster)
- Zoster incidence general population 4/1000 person years
  - 11/1000 in elderly. CMI declines at 4%/year of age
  - Incidence increased 30% in females
- SLE 6-32/1000 (all ages)
  - Mixed data whether immunosuppressive drugs increase
  - CMI decreased even if minimal immunosuppressives
- RA risk 1.5-2 fold
  - Increased with age, glucocorticoids, female, low functional status
  - 4.8/1000 no immunosupp, 14.3 on immunosupp
  - Increased risk: prednisone, leflunomide, azathioprine
  - Biologics: multiple studies no or minor increase risk TNFi, Tofa increased

What vaccine evidence do we have?

Pneumococcal vaccine

- Covers 88% of strains
- Effectively prevents infection in elderly and in RA patients on MTX (Coulsen et al ARD 2011)
- Overall ~20% non-response (>2 fold increase titre)
  - similar in RA and AIRD
- CDC ACIP recommends both (1) 13-valent pneumococcal conjugate vaccine and (2) 23-valent polysaccharide vaccine to adults with AIRD
- Boost in 5 years if under 65 when vaccinated

Influenza vaccine

- Effective AB responses in RA patients treated with TNFi: CZP (Kivitz J Rheum 2014)
- MTX impairs AB responses to INF and Pneumo vaccines (Hua et al, Arthritis Care Res 2013)
- Blunted Influenza vaccine response in SLE (Holvast ARD 2006)
- No evidence that influenza , tetanus toxoid or hepB vax trigger RA (1 million chart reviews: Ray et al Vaccine 2011)
- Conclusion: Vaccinate yearly for Influenza. If possible bring up to date before start MTX and definitely before Rituximab, but no need to stop Rx in order to vaccinate.

Varicella-zoster vaccine

- Live attenuated Japanese strain of VZV: safe and highly immunogenic, developed for leukemic children (2 doses)
- As VZV controlled by T cell mediated immunity, disease more severe and vaccine potentially a threat to patients with compromised T cell immunity
- Recommendations based on theoretical risks in absence of sufficient data
- Vaccine
  - Safe in children with leukemia (remission) and HIV (not severely immunocompromised)
  - Universal immunization in children in USA, Australia, Canada, Germany, Qatar, Korea, Saudi Arabia, Taiwan, Uruguay, Sicily, Madrid
  - FDA approved and CDC recommended >60 years.
- Outcomes
  - 51% reduction Zoster, 66% reduction post-herpetic neuralgia

VZV vaccine in treated AIRD patients

- Zhang et al JAMA 2012. Retrospective 463,541 ≥ age 60
- Autoimmune diseases, including RA (~60%), SpA, psoriasis and inflammatory bowel disease on DMARDs, steroids, biologics
- 4% received VZV vaccine
- Crude rate HZ within 42 days = 7.8 cases/1,000 person years
- Non-vaccinated 11.8 cases/1,000 person years
- Vaccinated on biologics = 0 cases
- Hazard ratio after multivariate adjustment = 0.6
- 42 cases Zoster within 42 days none disseminated.

- Chetham Mayo Clin Proc 2015. Retrospective 633 on biologics
- None developed Zoster within 42 days and protection was 40%

- Double blind trial on TNFi is enrolling: VZV CMI, Zoster rates

VZV vaccine recommendations and horizon

- Immunize immunocompetent RA patients >50
  - NB vaccination rates are low
- Contra-indicated in immunosuppressed patients
  - Prednisone >20mg/day, leflunomide, azathioprine, cyclophosphamide
  - Biologics
  - In practice in Australia, immunize soon after diagnosis prior to use of biologics
- On horizon
  - GSK subunit liposomal vaccine completed phase 3
  - Excellent induction CMI. Zoster protection >95%
  - Risk to AIRD patients not tested, needs trial

Yellow fever vaccine

- Travel to endemic areas in Africa
- Highly effective vaccine, relies on neutralising antibodies
- Few studies in immunocompromised but generally contra-indicated
- HIV patients – meta-analysis of 484 patients, no infectious complications, reduced AB titres (Barte 2014, Cochrane Review)
- Reduction associated with lower CD4 counts and higher HIV titres
- 19 allograft recipients – no serious adverse effects
- Conclusion: consider on case-by-case basis

Our case: What is the risk?

- History of chickenpox or zoster?
- Previously vaccinated?
- If naïve, patient is immunocompetant

EULAR recommendations vaccination 2010

- Vaccination is the most effective way to prevent infection in AIRD patients
- Vaccination check during history in the initial work-up of patients
  - *Haemophilus influenzae* b
  - Hepatitis A
  - Hepatitis B
  - Human papillomavirus
  - Influenza
  - *Neisseria meningitides*
  - Rubella (for women of childbearing age)
  - *Streptococcus pneumoniae*
  - Tetanus toxoid

EULAR recommendations 2010

- Bring immunisations up to date: ideally during stable disease.
- Vaccination can be administered during the use of DMARDs and bDMARDs but ideally before starting B cell depleting biological therapy.
- Strongly consider inactivated influenza and 23 valent polysaccharide pneumococcal vaccination.
- Tetanus toxoid vaccination in accordance to recommendations in general populations except in patients who have received Rituximab within last 24/12, should receive tet tox with major/contaminated wounds.

Advisory Committee on Immunization Practices (ACIP USA)

- Travellers with AIRD:
  - Vaccinations according to general rules except for live attenuated vaccines.

EULAR recommendations 2010

- Other vaccines
  1. HPV:
     - More common in patients with SLE.
     - Low rate of spontaneous clearance so high risk of developing cervical cancer.
     - Vaccination should be considered for females with SLE until age of 25 if not sexually active

     - needs to be before infection.
  2. Hepatitis A and/or B : Only in at risk population, only when protective antibodies are absent.
  3. BCG: Not recommended.

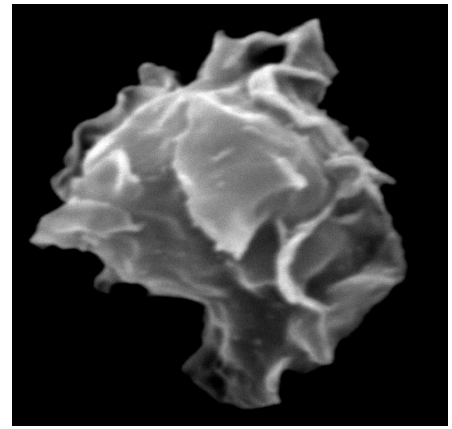
Why we need antigen-specific therapy

- Rheumatoid arthritis unmet needs
  - Avoid suppression of immunity to infection or cancer
  - Long-term drug-free remission (compliance)
  - Incomplete response and adverse events current drugs
    - poor stratification using biomarkers
  - Lower cost of treatment
  - Prevention in at-risk subjects

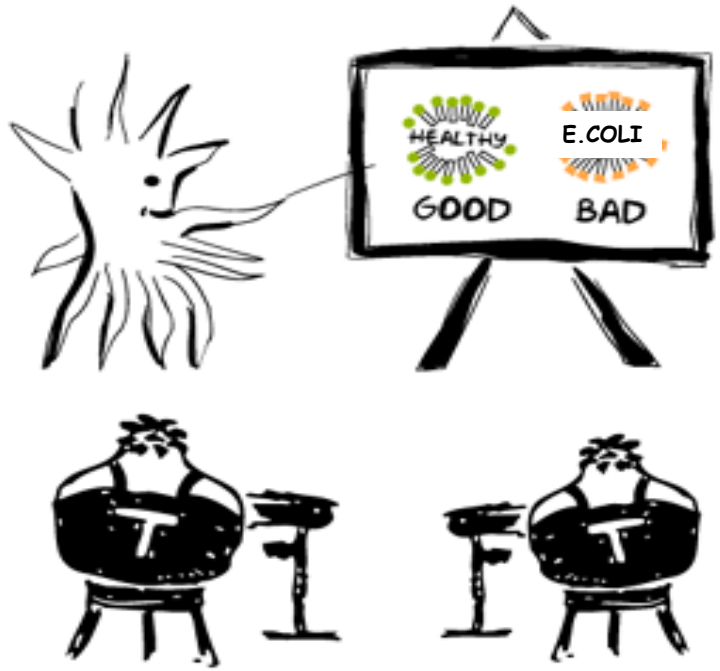
- Other AIRD with similar needs

RelB-deficient dendritic cells promote antigen-specific tolerance

- RelB-deficient dendritic cells, or DC generated in presence of NF-κB inhibitor exposed to antigen suppress primed immune responses.
- CD4+ antigen-specific regulatory cells transfer tolerance, IL-10 dependent. Martin E et al: Immunity 2003.
- POC antigen-induced arthritis. Martin, Arthritis Rheum 2007

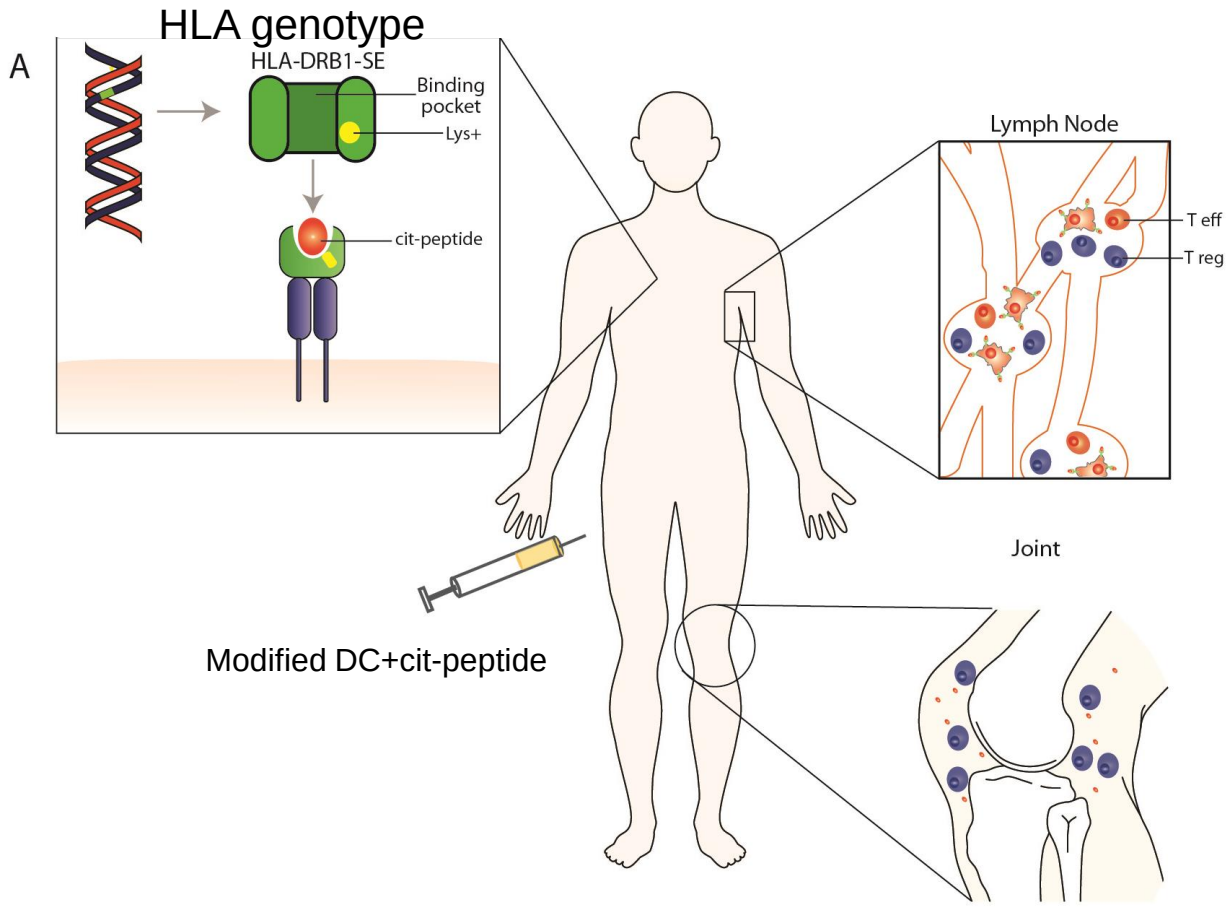


What has changed?

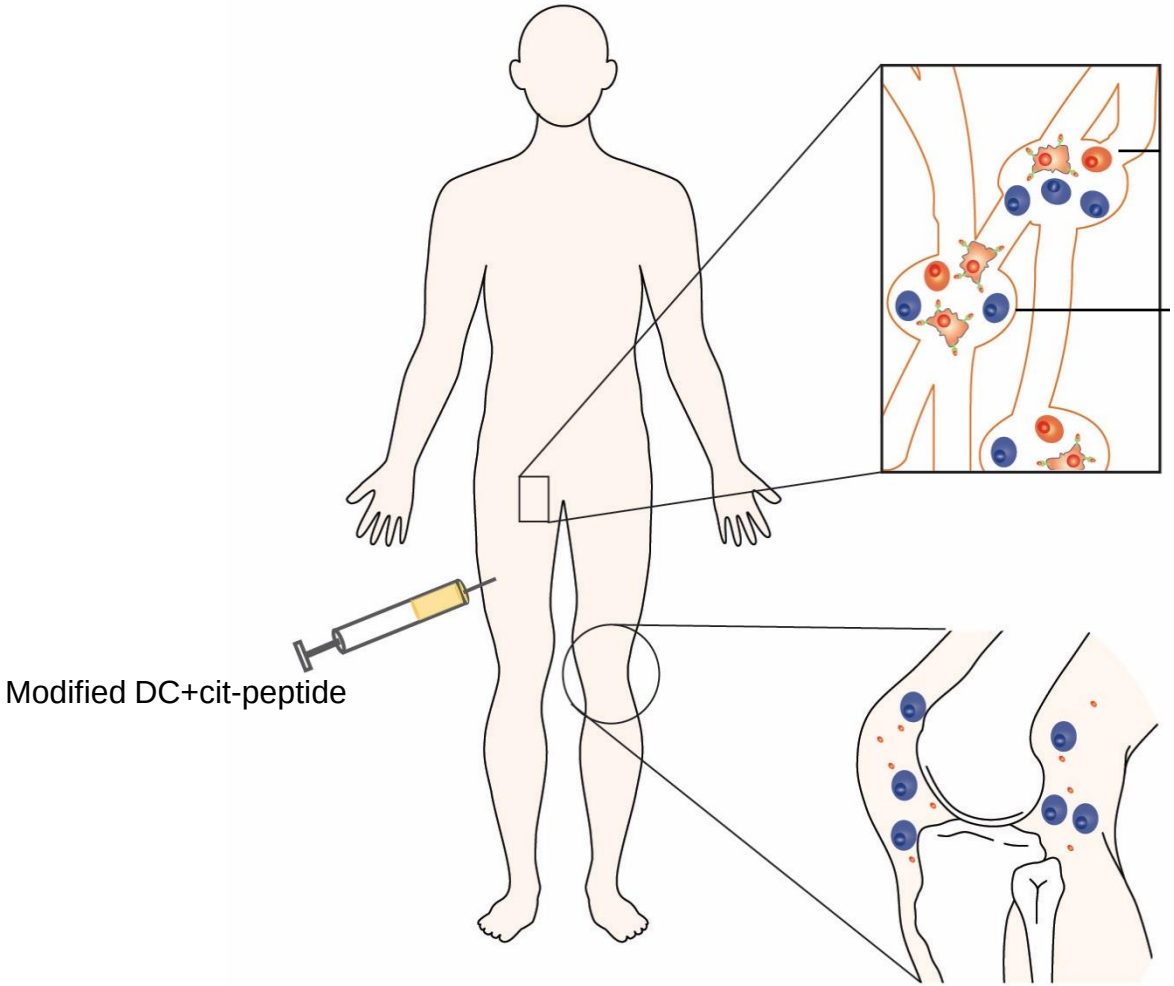


- Target the conductors of the orchestra
- Dendritic cells can be targeted to activate or silence the immune system to specific antigens
- Unique functions: unique targeting postcodes
- From vaccines against infectious antigens to autoimmune and cancer antigens

Translation 2003-2017: The concept in rheumatoid arthritis



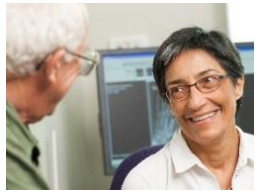
DC immunotherapy decreased effector T cells and inflammation

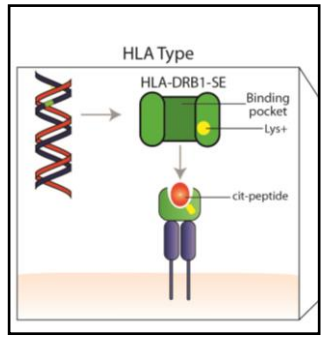


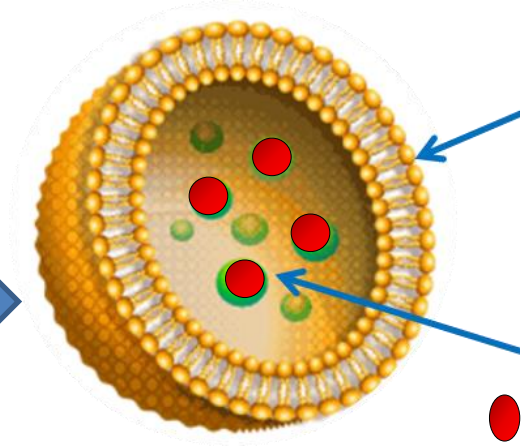
Inflammation ↓
Autoantibodies ↓

Benham H et al. Science Transl Med 2015

What antigen-specific immunotherapy for RA looks like





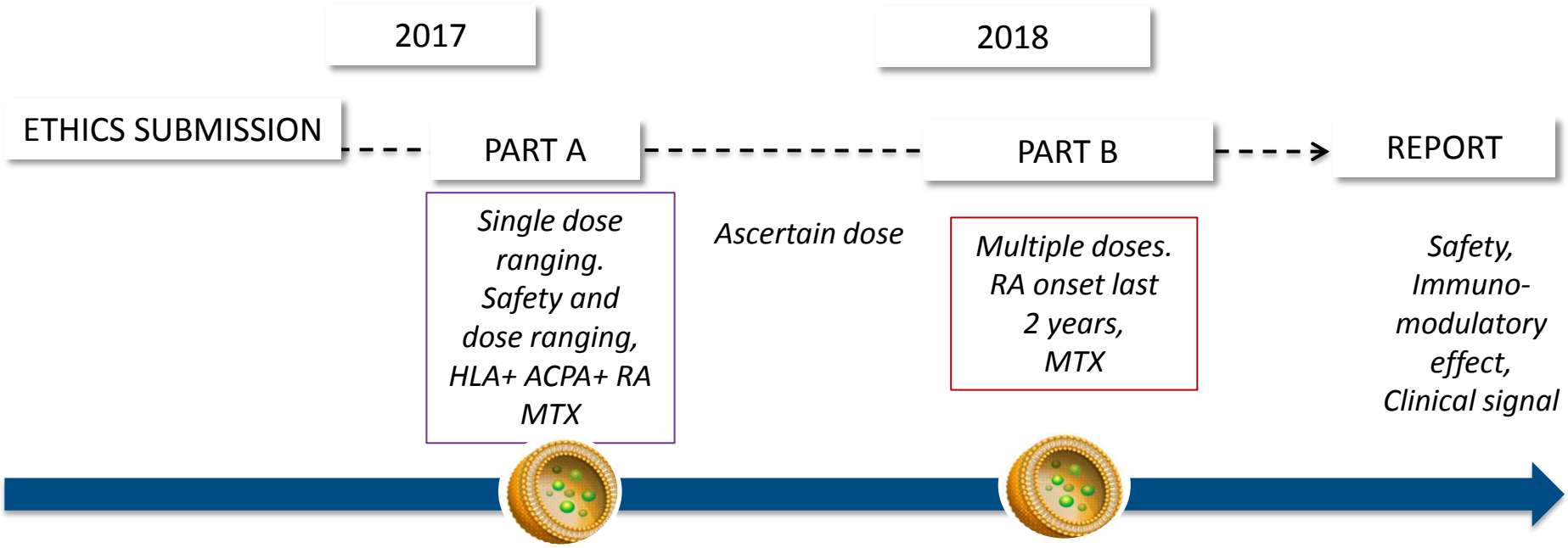


Phospholipid bilayer entraps vitamin D3 inhibitor

Aqueous core entraps RA antigen specific to genotype

Germline single genetic test, immunodiagnostic

Phase 1 clinical trial timeline RA



ACPA+ RA referral and screening

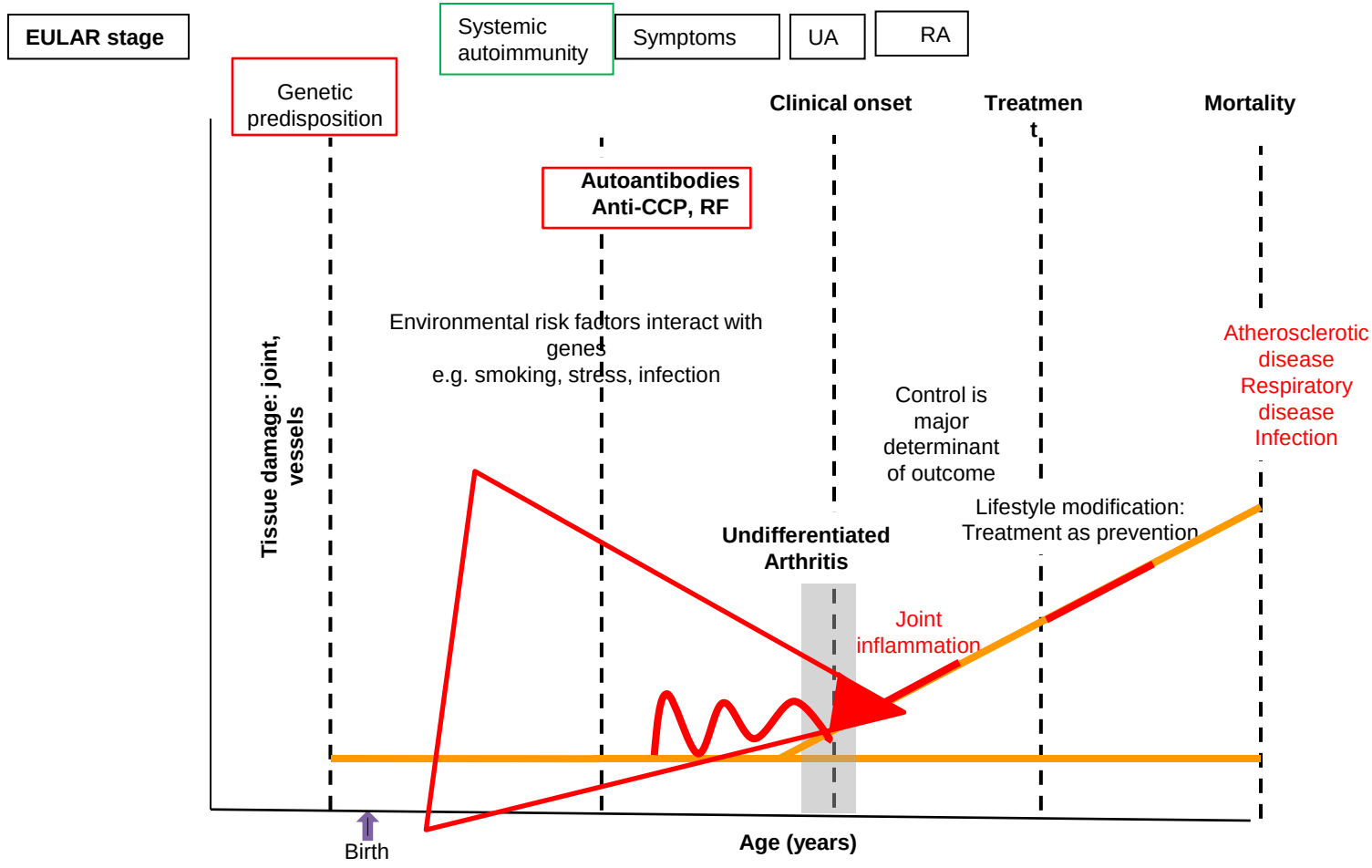
dendright

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

The benefits and challenges of personalised nanomedicine

- The specificity of vaccines: less toxic, individually tailored, prevention
- Reduced manufacturing costs and longer duration of action: more affordable, better compliance
- Diagnosis requires genotyping and immunodiagnostics
- Differs from current clinical practice: pick up early disease and high risk: family, population or high-risk screening
  - Please refer patients with arthralgia/intermittent swelling and anti-CCP: di.arthritis@uq.edu.au
- Planning trials of prevention for full-blown RA

If Immunotherapy were available for RA could we find the population in need?



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