The Immunopathogenesis of Rheumatoid Arthritis and Immunologically Targeted Therapy

Alan L. Epstein, MD
Clinical Professor of Medicine
University of Pennsylvania School of Medicine

Disclosures

Speakers' Bureau and Consultant:

Abbvie, Amgen, Astra-Zeneca, BMS, Chemocentryx, Fresenius Kabi, GSK, Janssen, Lilly, Novartis, Pfizer, Quest, Sanofi

Learning Objectives

The Immunopathogenesis and Immunologically Targeted Treatment of Rheumatoid Arthritis

Abnormal immune responses are the cause of many of our inflammatory diseases with serious morbidity and mortality. Antibodies are in widespread use to treat immunologic diseases. Understanding immunology helps us to better understand the diseases that we treat and their therapies.

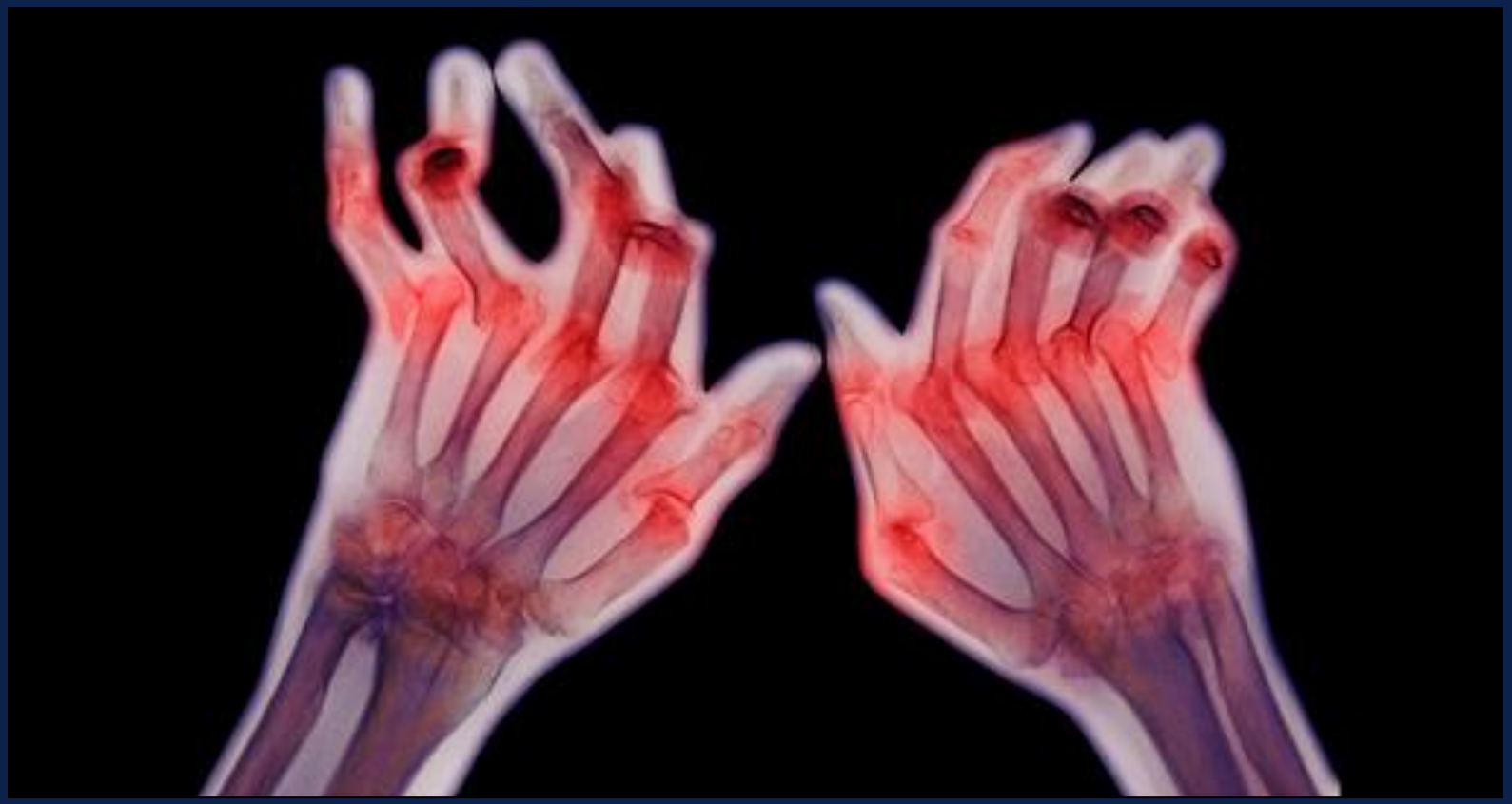
- 1) Review the immunopathogenesis of rheumatoid arthritis
- 2) Discuss the concept of preclinical rheumatoid arthritis.
- 3) Review the immunologic heterogeneity of rheumatoid arthritis.
- 4) Discuss the immunologically targeted treatment of rheumatoid arthritis.

When thinking about our patients with immune mediated inflammatory diseases we need to address 2 questions:

- How do perturbations in the normal immune system result in disease?

- How can we modulate the abnormal immune response to help our patients?

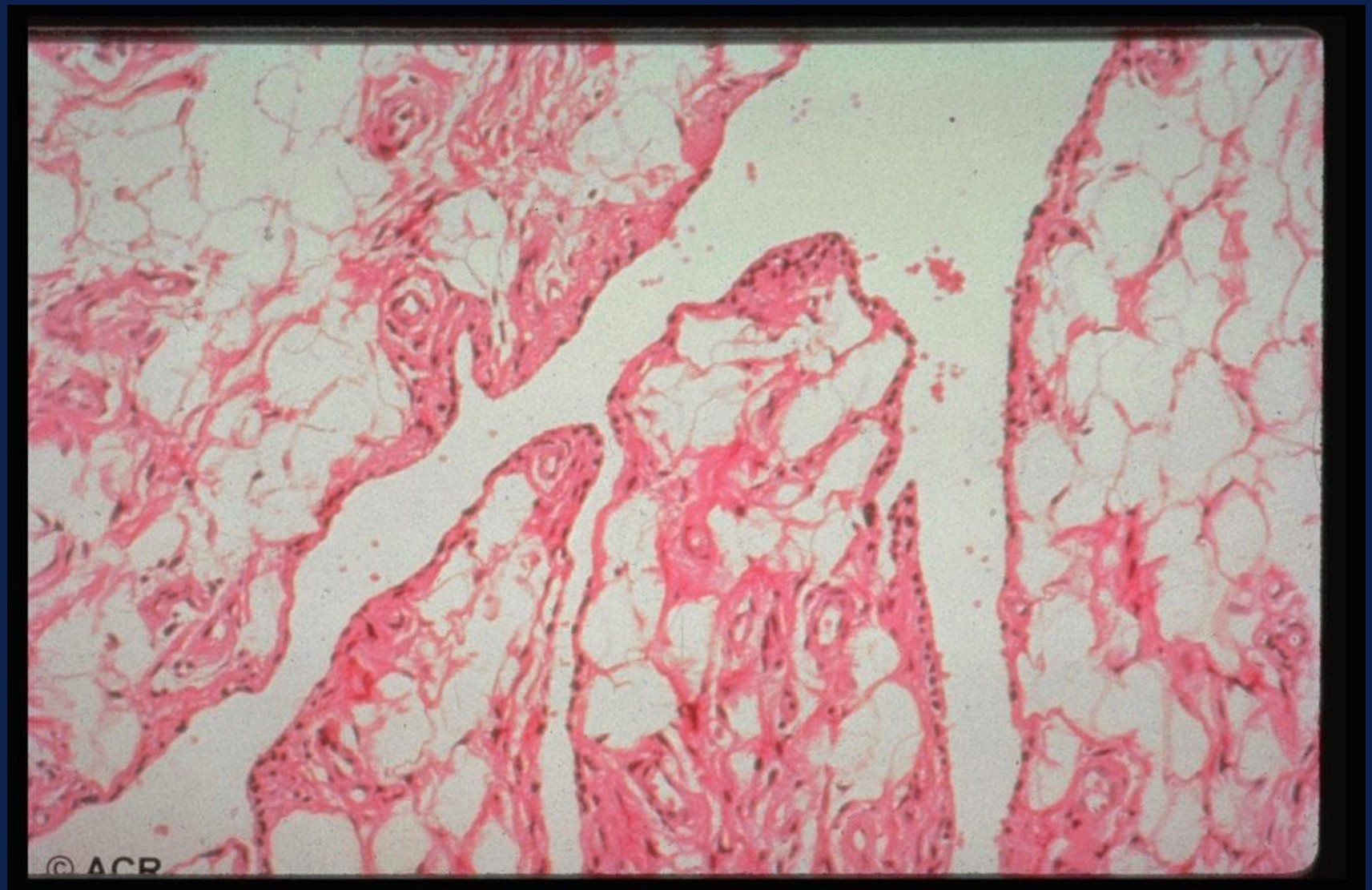
What is rheumatoid arthritis?



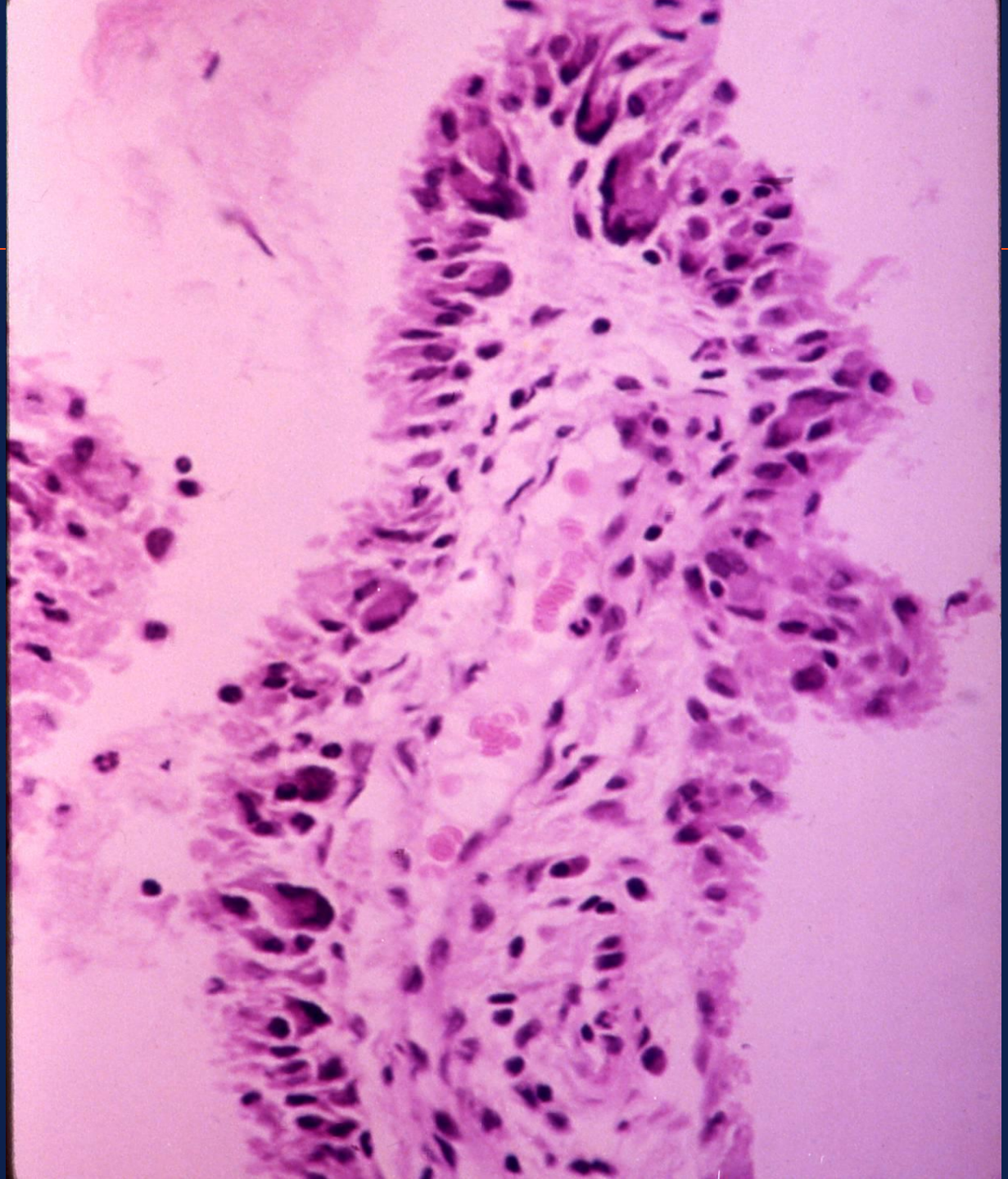
Rheumatoid Arthritis is:

- An inflammatory disease
- A destructive disease
- A systemic illness that can involve internal organs
- High incidence of co-morbidities leading to increased mortality (cardiovascular, infection, malignancy)
- **When thinking about the immunopathogenesis of RA we need to account for all these aspects of the disease**

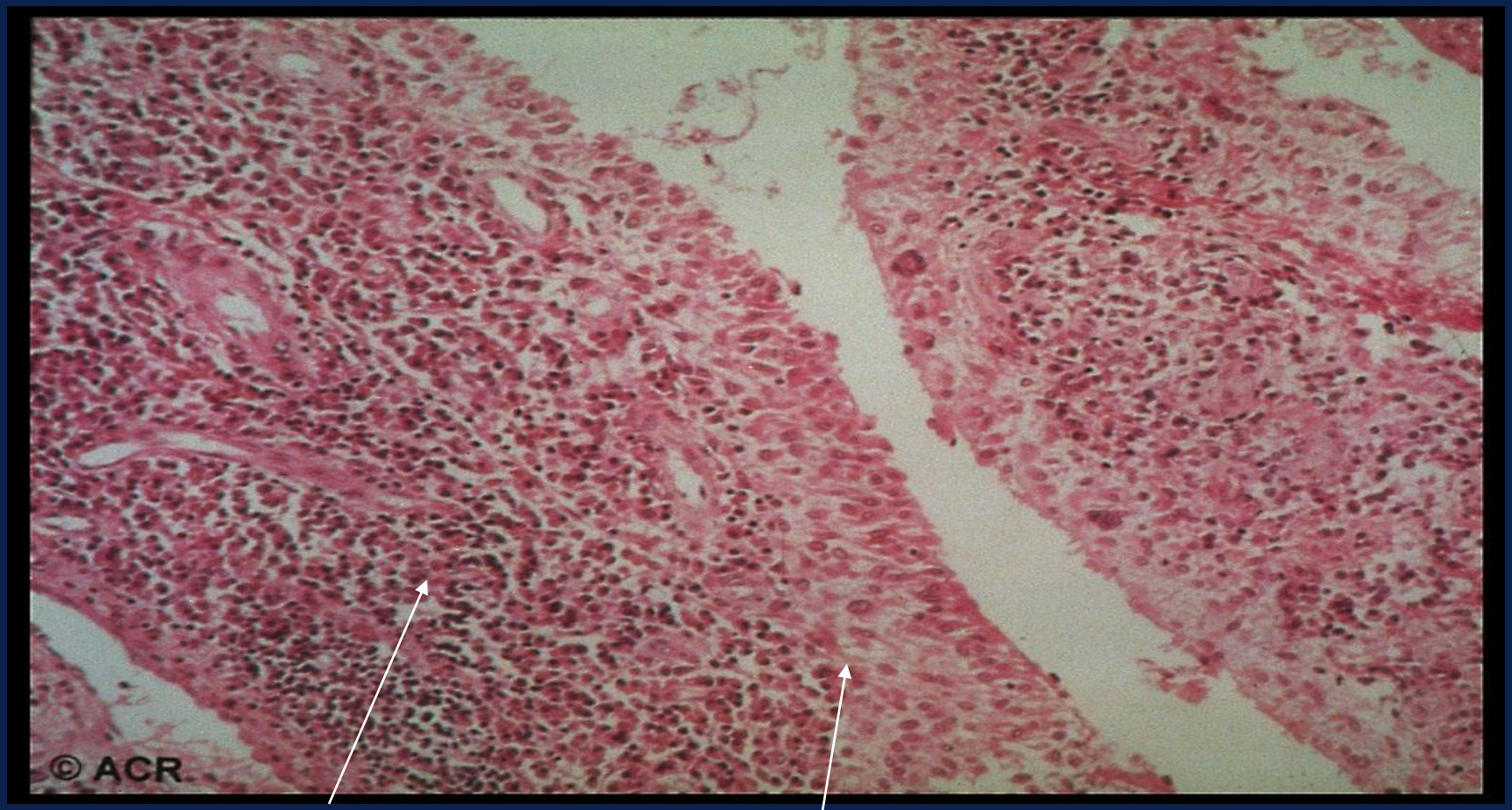
Normal Synovium



Very Early RA



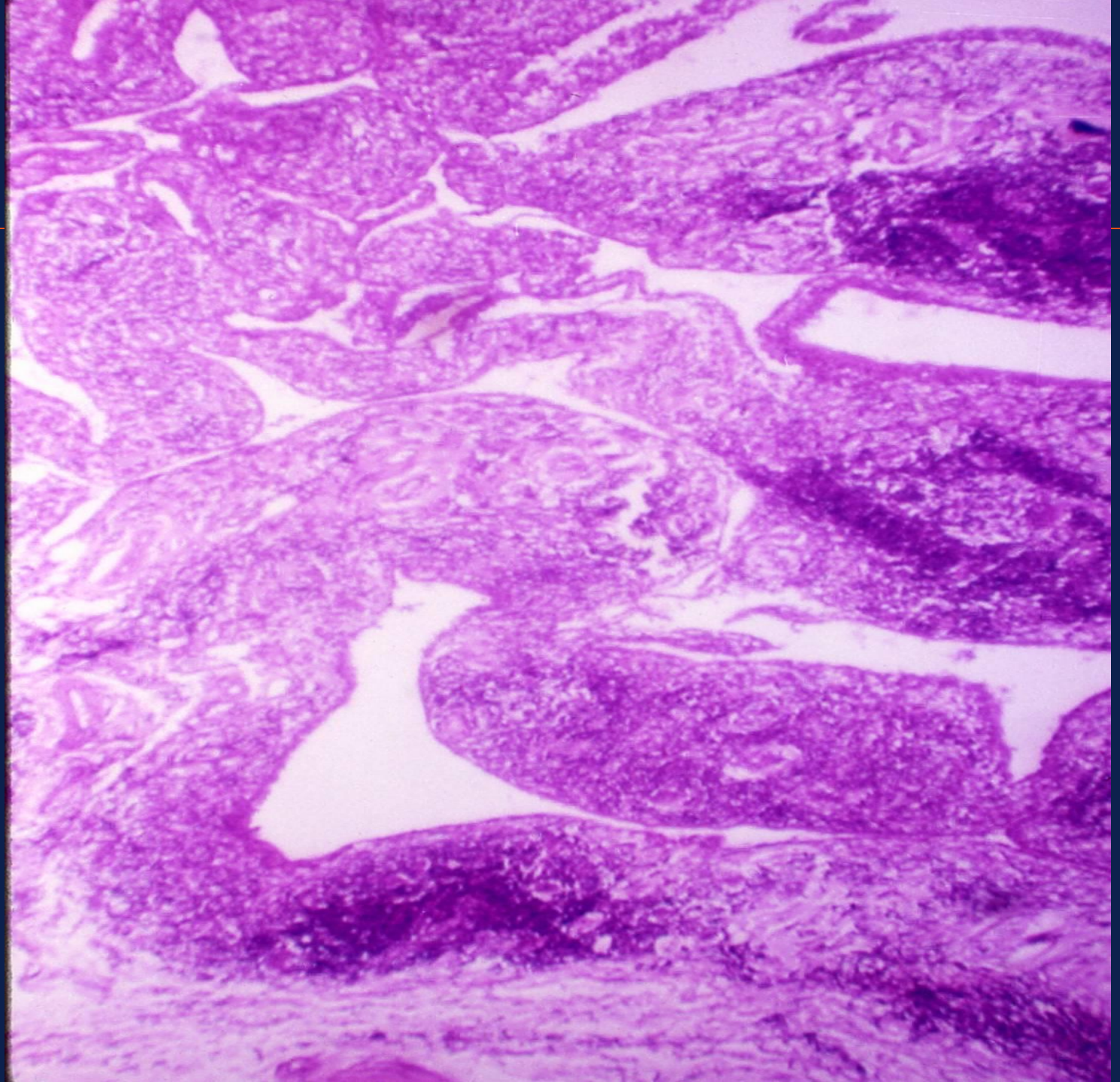
Rheumatoid Synovitis



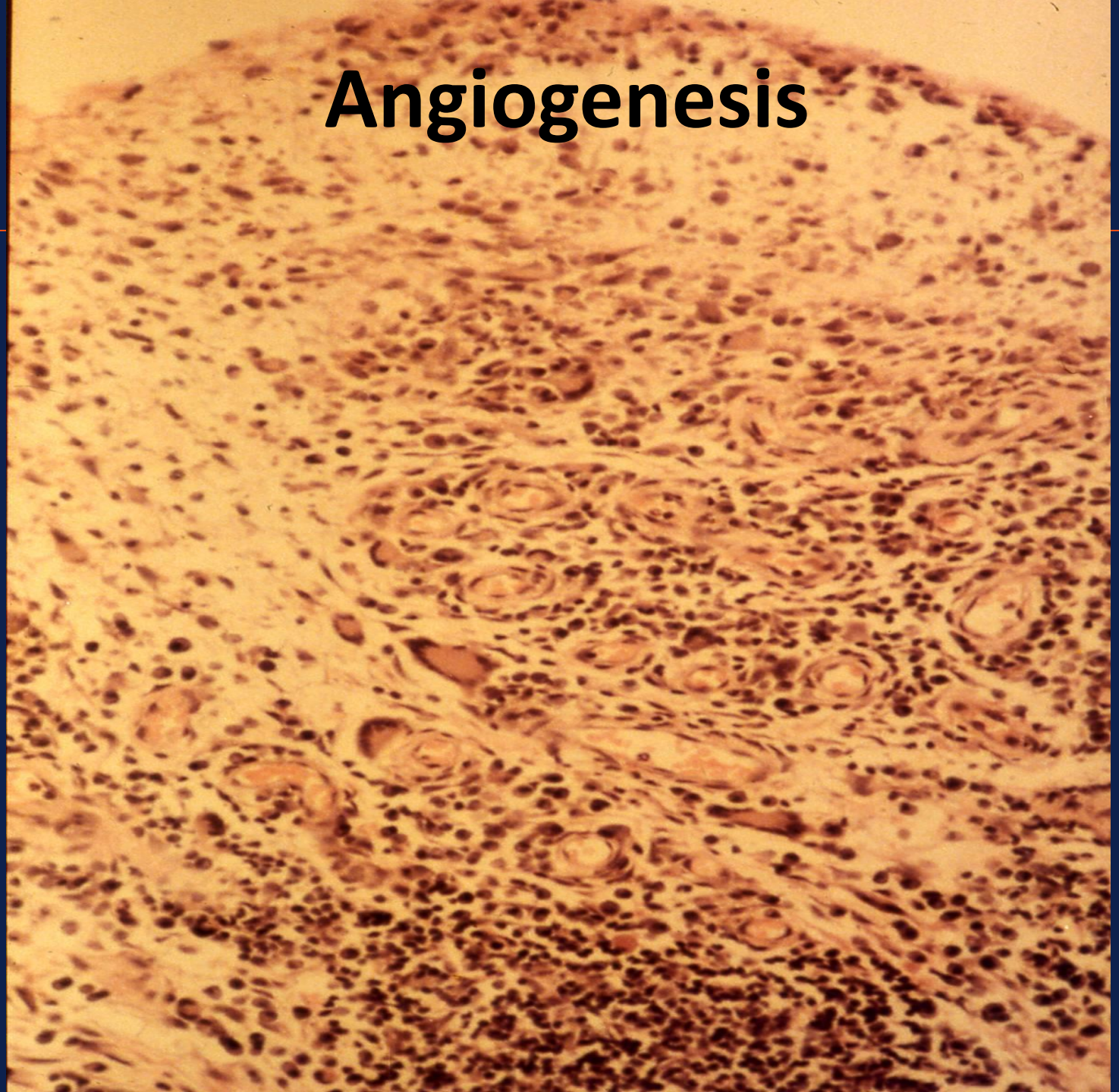
Lymphocyte recruitment into subsynovial space

Hyperplasia of synovial lining cells

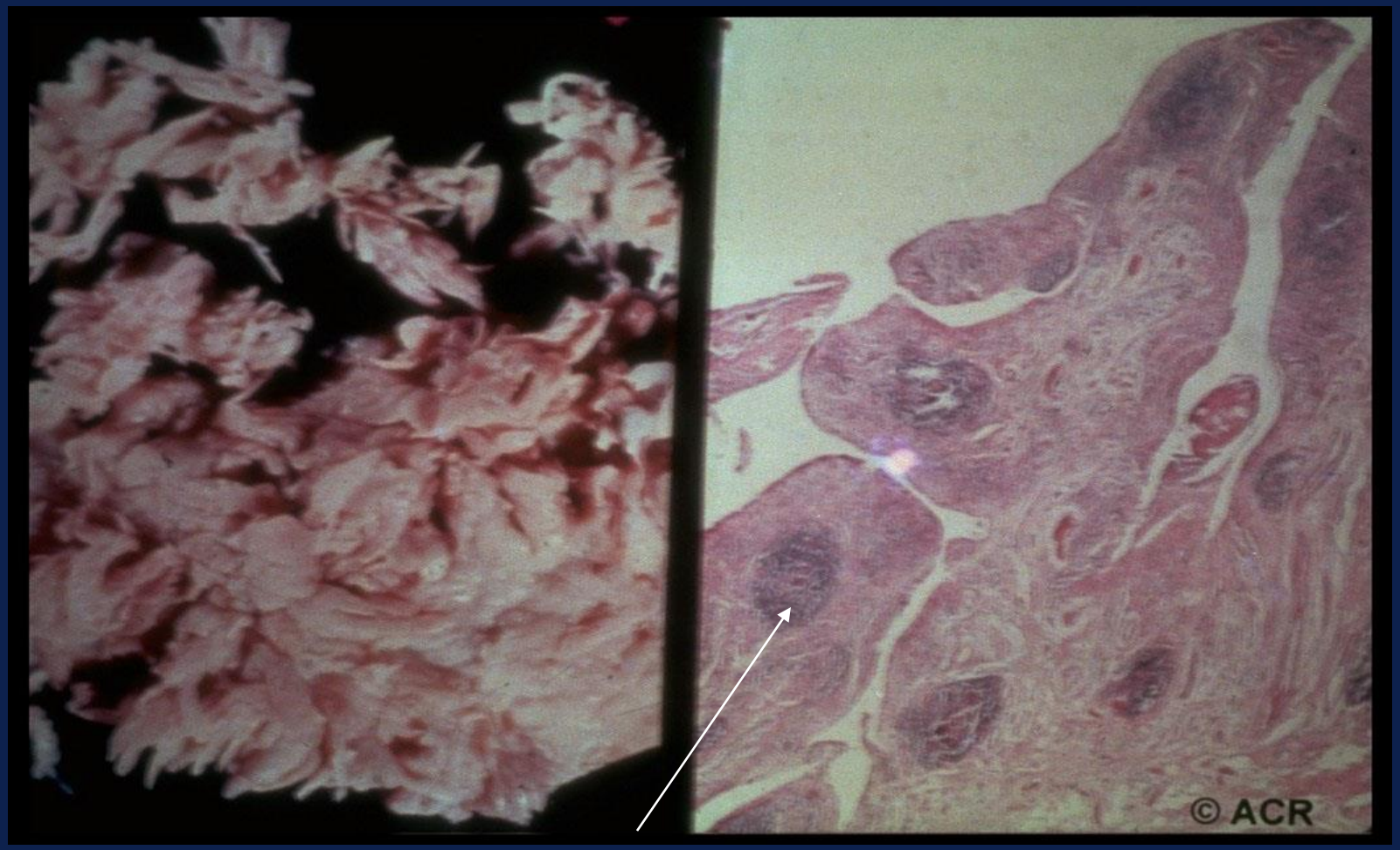
Later RA



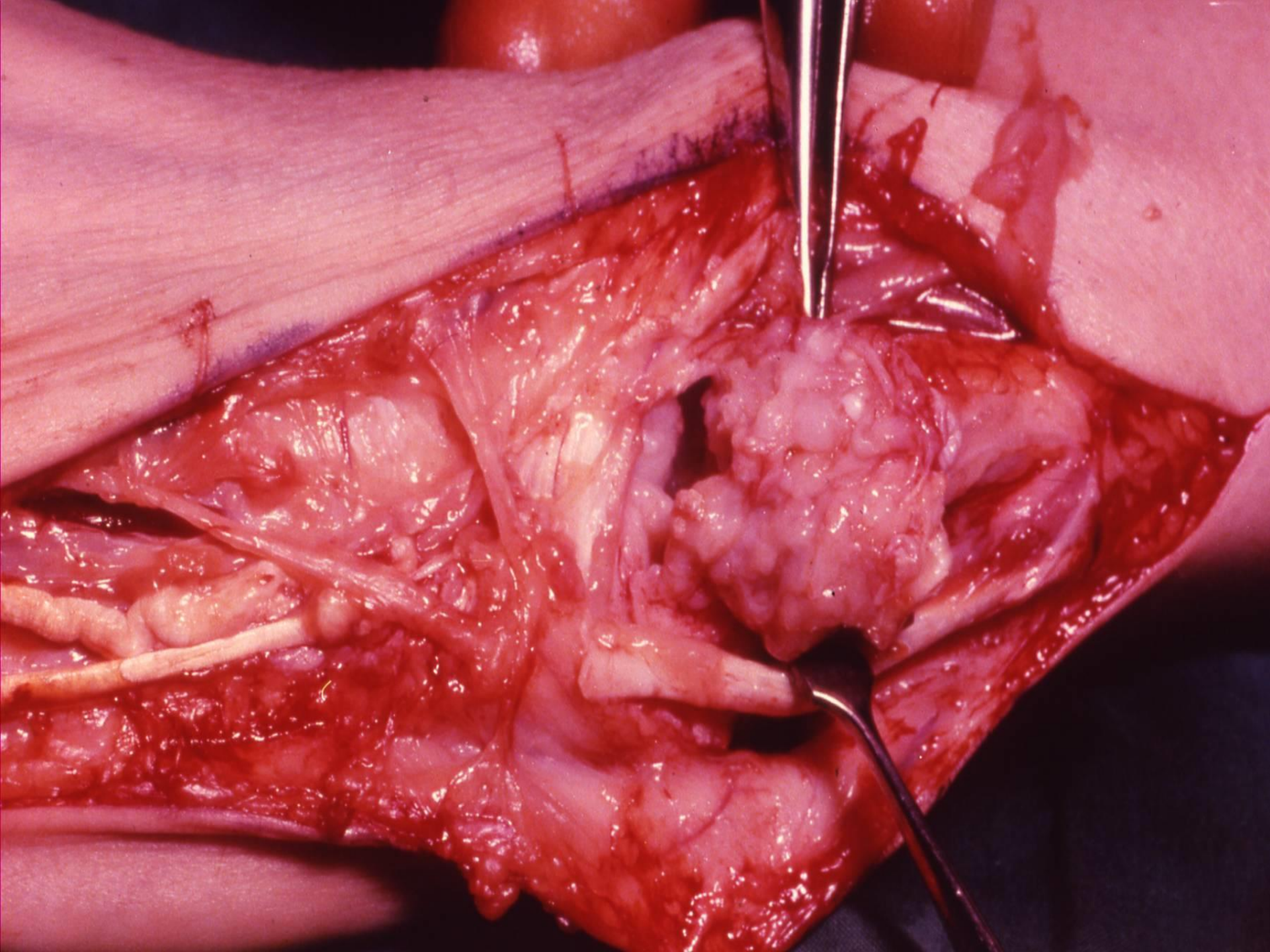
Angiogenesis



Rheumatoid Synovitis



Prominent nodal lymphoid architecture



Insights into the Initiation and Progression of RA

Etiopathogenesis of RA

- Genetic predisposition
  - *HLA-DRB1* [1]
  - *PTPN22* [2]
- Environment
  - Prior infections [3]
  - Hormones [4]
  - Smoking [5]
- **Involves the entire integrated immune response**[3]
  - CD4+ helper T cells [6]
  - B cells, plasma cells, and autoantibodies [7-9]
  - Innate immune system
  - Proinflammatory cytokines: TNF-α, IL-1, IL-6, IL-17, others [9]

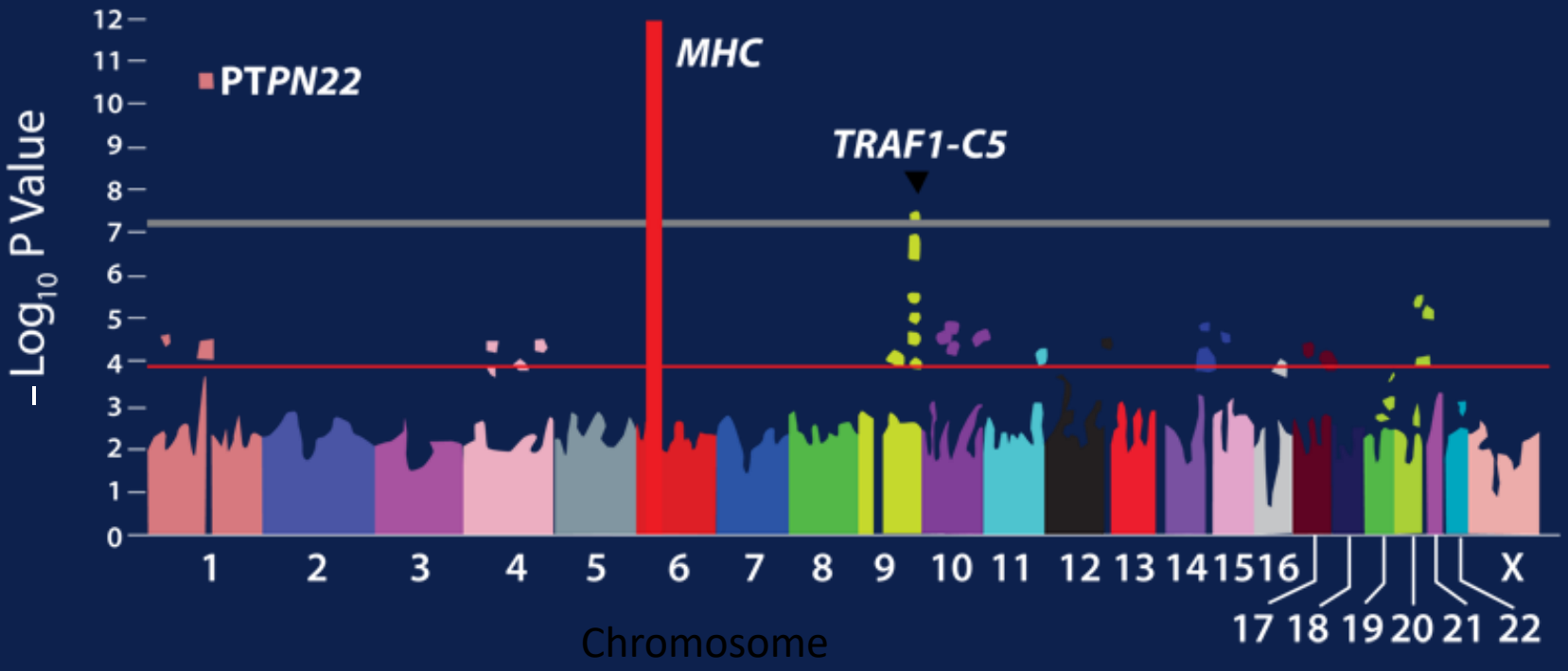
Tayo BO, et al. *BMC Med Genet.* 2009;10:142.
Chen L, et al. *BMC Proc.* 2009;3 Suppl 7:S6.
Haier J. *Rheumatology.* 1999;38(6):504-9.
Karlson EW, et al. *Arthritis Res Ther*. 2009;11(3):R97.
Stolt P. *Ann Rheum Dis.* 2003;62(9):835-41.
Evans HG, et al. *Proc Natl Acad Sci U S A.* 2009;106(15):6232-7.
Nanki T, et al. *Arthritis Res Ther.* 2009;11(5):R149.
Roll R, et al. *Arthritis Rheum*. 2006;54(8):2377-86.
Hueber W, et al. *Arthritis Res Ther. 2009;11(3):R76.*

★

Genome-wide Association Studies (GWAS)*

HLA and non-HLA genes have been linked to ACPA-Positive Disease

Genetic studies have identified more than 100 polymorphisms conferring risk



The grey horizontal line indicates SNPs that are significant at a genome wide level

*SNPs plotted according to chromosomal location, with the -log10 P values corrected with the use of genomic control

SNPs=single nucleotide polymorphism; MHC=major histocompatibility complex;
TRAF1=TNF signal transduction gene; *C5*=complement 5 gene
PTPN22=tyrosine phosphatase –associated with B and T cell regulation

Plenge RM et al. *N Engl J Med.* 2007;357(12):1199-1209.

Genetic Predisposition to RA

Genetic polymorphisms confer 30-60% of overall risk

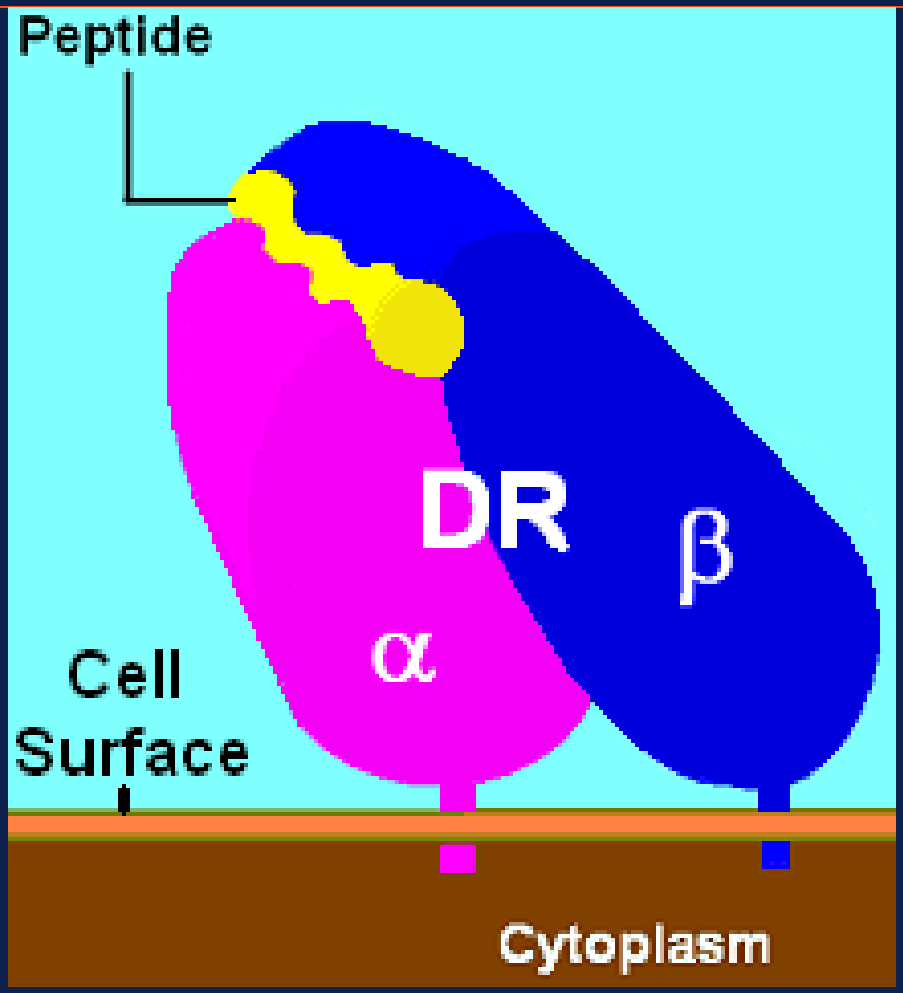
- **Strongest genetic factor associated with an increased risk of developing RA**:
  - Polymorphisms at the ***HLA-DRB1*** locus (chr. 6p21.3)
  - ***Encodes for the β-chain*** of the MHC class II molecule[1]

    Proteins involved in antigen presentation to T cells [2]
- **MHC molecules containing the shared epitope (AA residues 71-74 of the β-chain) are able to accommodate citrullinated peptides in the binding site**

Tayo BO, et al. *BMC Med Genet.* 2009; 10:142.
Weyand CM, et al. *J Clin Invest.* 1992; 89(6):2033-9.

★

Shared Epitope--part of the binding site of an MHC class II molecule



- **MHC molecules containing the shared epitope are able to accommodate citrullinated peptides in the binding site**

Environment and RA

Factor[1]	Risk Factor[1]	Defensive Factor[1]
Sex hormones	Estrogen	Testosterone
		Oral contraceptives[2]
Pregnancy		Pregnancy
Infections	Human Parvovirus B19 Epstein-Barr virus Hepatitis B virus Mycoplasma *Mycobacterium tuberculosis*	
Smoking	**Smoking**	

Adapted from Kobayashi S, et al. *FEBS J.* 2008;275(18):4456-62.
Brennan FM, et al. *Arthritis Res Ther.* 2008;10(2):R36.

Environmental factors may contribute to the development of RA

- Smoking
  - Smokers are more than twice as likely to develop seropositive disease as age matched controls[1]
  - Dose dependent relationship between ACPA + disease and duration and quantity of tobacco use[2]

1. Padyukov L et al. *Arthr & Rheum.* 2004;50(10):3085-3092.
2. Klareskog L et al. *Arthritis Rheum.* 2006;54(1):38-46.

Other environmental factors that increase risk of RA

- Bacteria in Lungs[1]
- Gingival Disease (Chronic Periodontitis)[2]
- Silica exposure[3]
- Air Pollutants[4]
- Viruses[5]
- Gut flora[6]

1. Liao F et al. *Medical Hypotheses.* 2009;72:732–735.
2. Rosenstein ED et al. *Inflammation.* 2004;28(6):311-318.
3. Wegner N et al. *Arthritis Rheum.* 2010;62(9):2662-2672.
4. Caplan A. *Thorax.* 1953;8:29-37.
5. Costenbader KH et al. *Arthritis Research & Therapy.* 2006;8:204
6. Kerr JR. *Ann Rheum Dis.* 2000;59(9):672-683.

TOLERANCE

Immunologic Tolerance

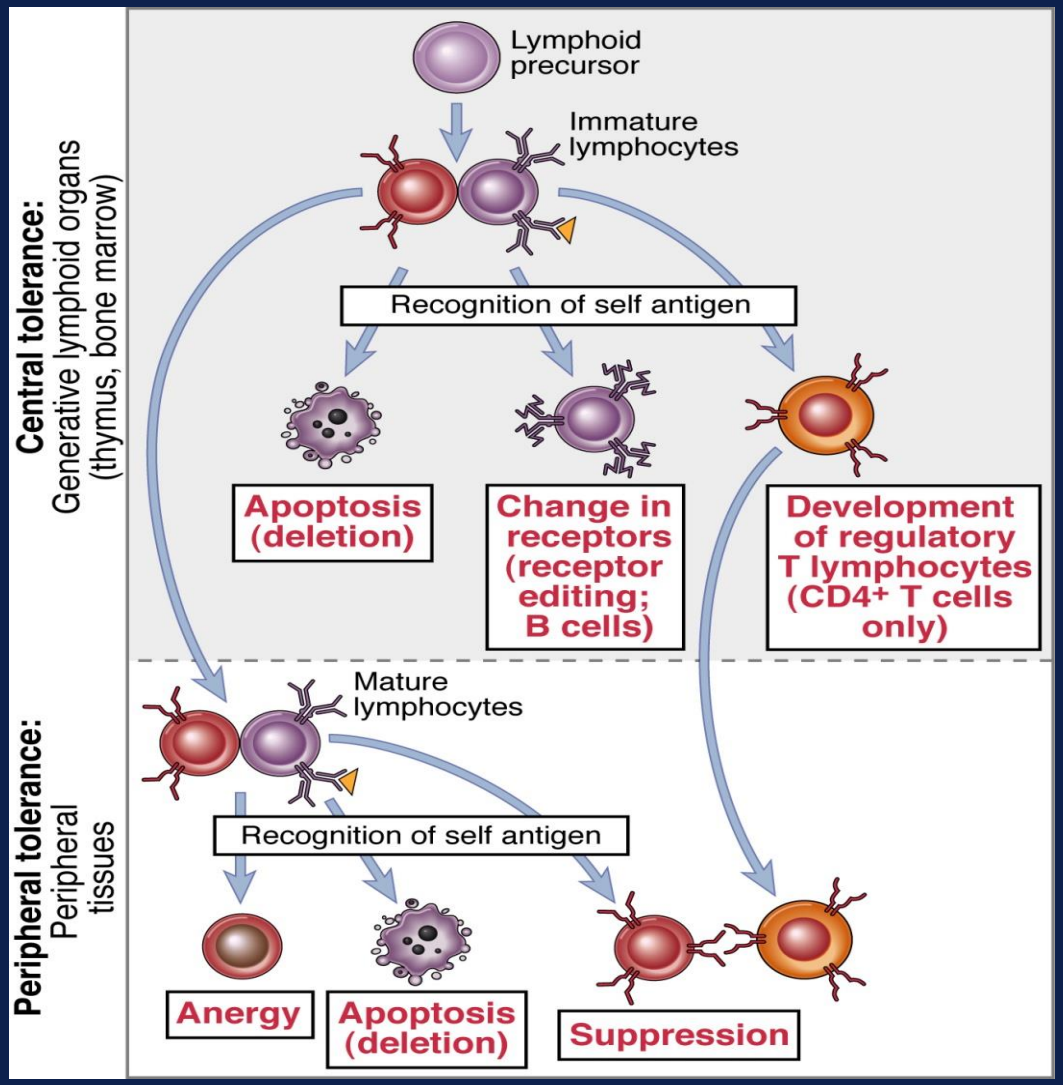
- Definition:
  - **specific unresponsiveness to an antigen** that is induced by exposure of lymphocytes to that antigen

- Significance:
  - **All individuals are tolerant of their own antigens (self-tolerance);**
  - **Breakdown of self-tolerance results in autoimmunity**

From Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007

Central and peripheral tolerance

Central Tolerance:



From Abbas, Lichtman and Pillai. Cellular and Molecular Immunology 6th ed, 2007

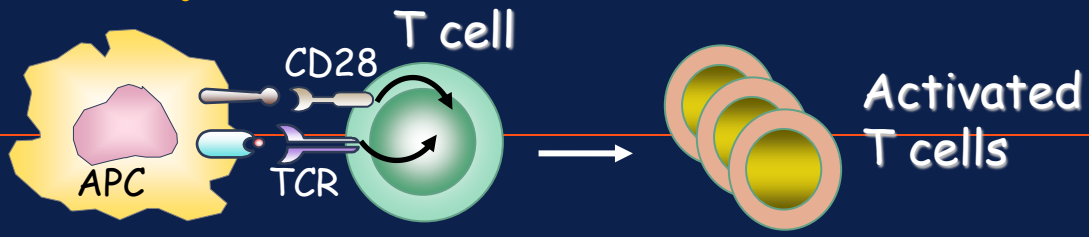
The principal fate of lymphocytes that recognize self antigens in the generative organs is death (deletion), BUT:

Some B cells may change their specificity (called "receptor editing")

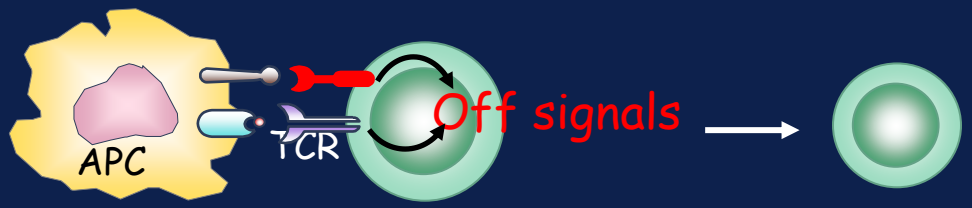
Some CD4+ T cells may differentiate into regulatory (suppressive) T lymphocytes

Peripheral tolerance

Normal T cell response

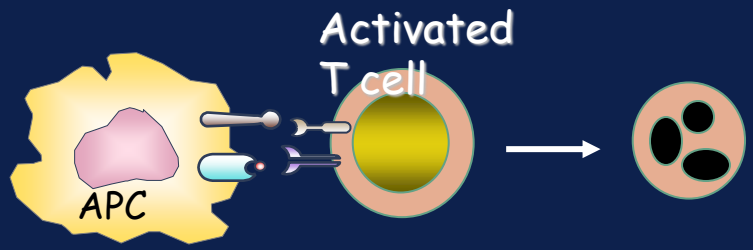


Anergy



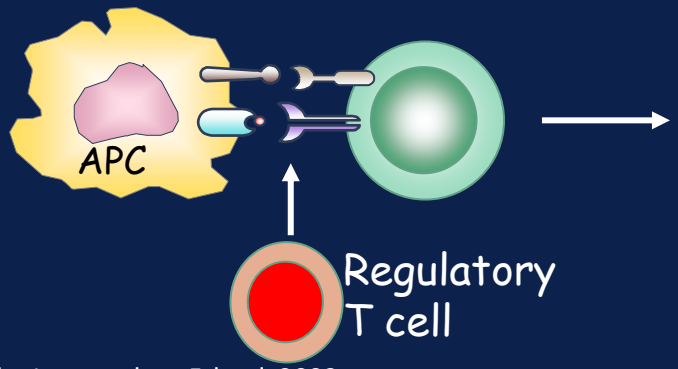
Functional unresponsiveness

Deletion



Apoptosis (activation-induced cell death)

Suppression



Block in activation

From: Abbas & Lichtman, Cellular & Molecular Immunology 5th ed 2003

HOW IS TOLERANCE BREACHED??

IE-WHY DOES THE RA PATIENT RECOGNIZE SELF AS FOREIGN??

PADI* Citrullination is the Target Resulting in Breaching Tolerance in RA

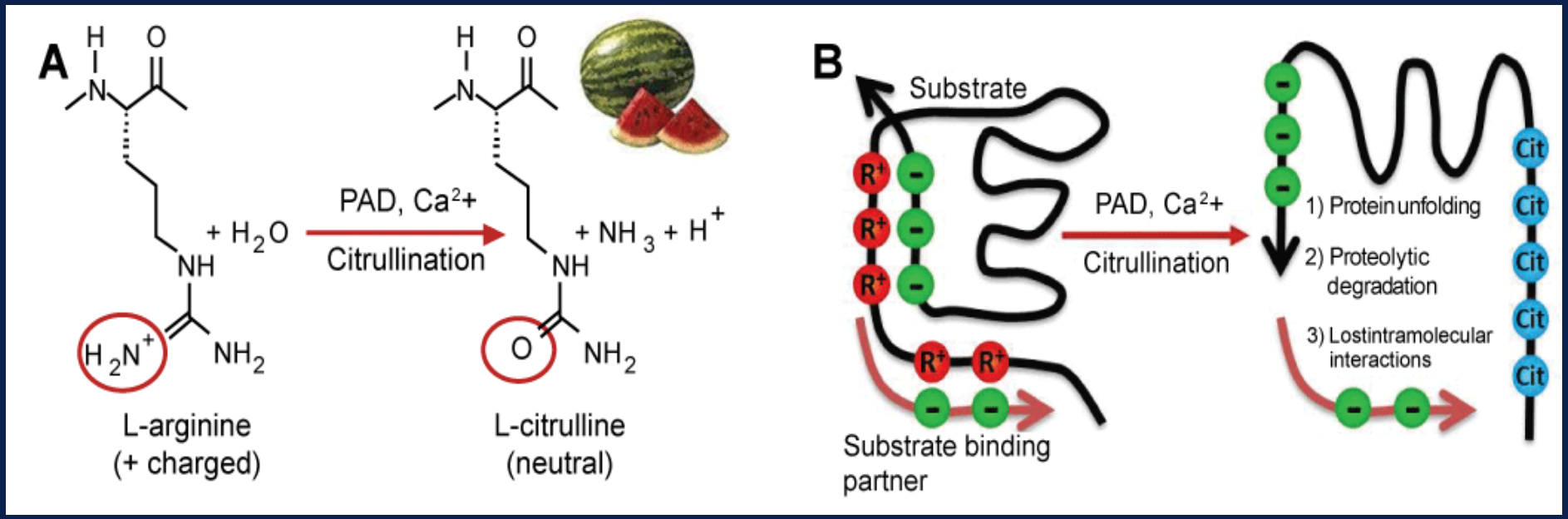
- Citrullination occurs at sites of inflammation[1]
- PADI post-translationally modifies proteins[1-3]
- Peptidyl **arginine** amino acid residues are modified to **citrulline** residues[1-3]
- This process occurs in multiple proteins[3]

RA in most patients characterized by autoantibodies that target citrulline-containing proteins

*PADI=peptidyl arginine deiminase

1. Sokolove J, et al. *Arthritis Rheum.* 2011;63(1):53-62.
2. Beltrami A et al. *J Bio Chem.* 2008;283(40):27189-27199.
3. Snir O et al. *Ann Rheum Dis.* 2009;68(5):736-743.

CITRULLINATION

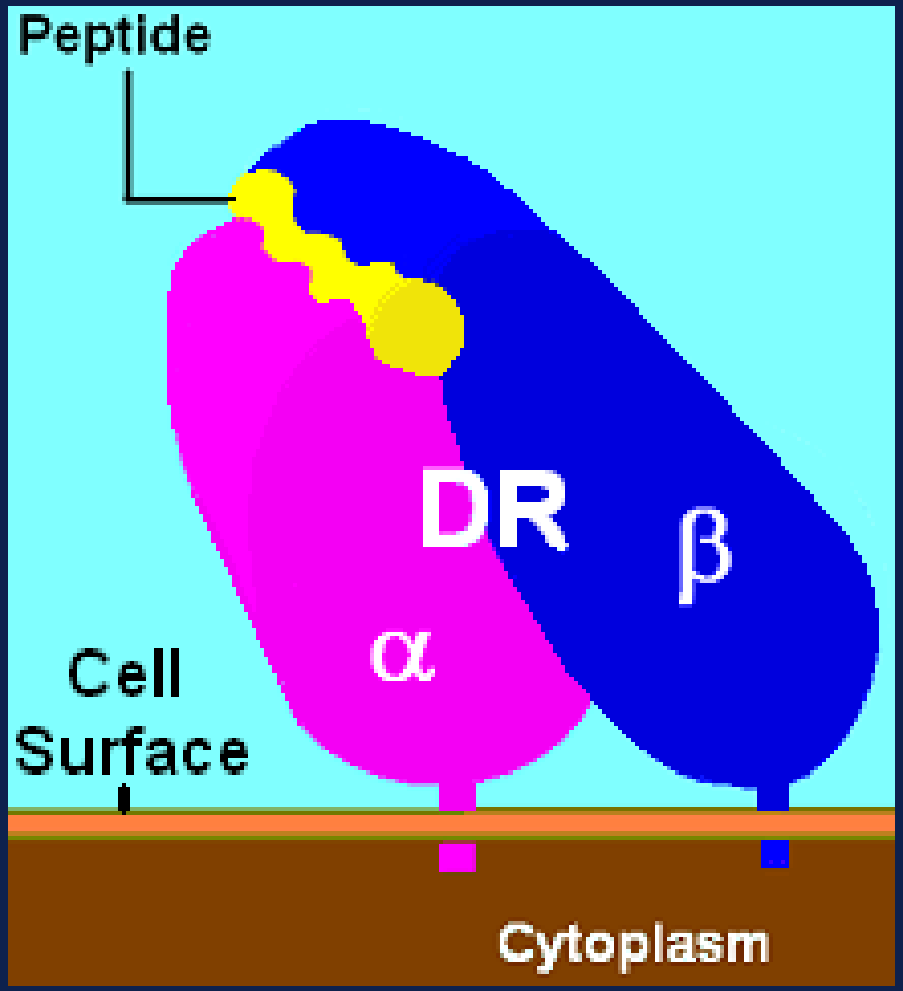


Tertiary structure changed

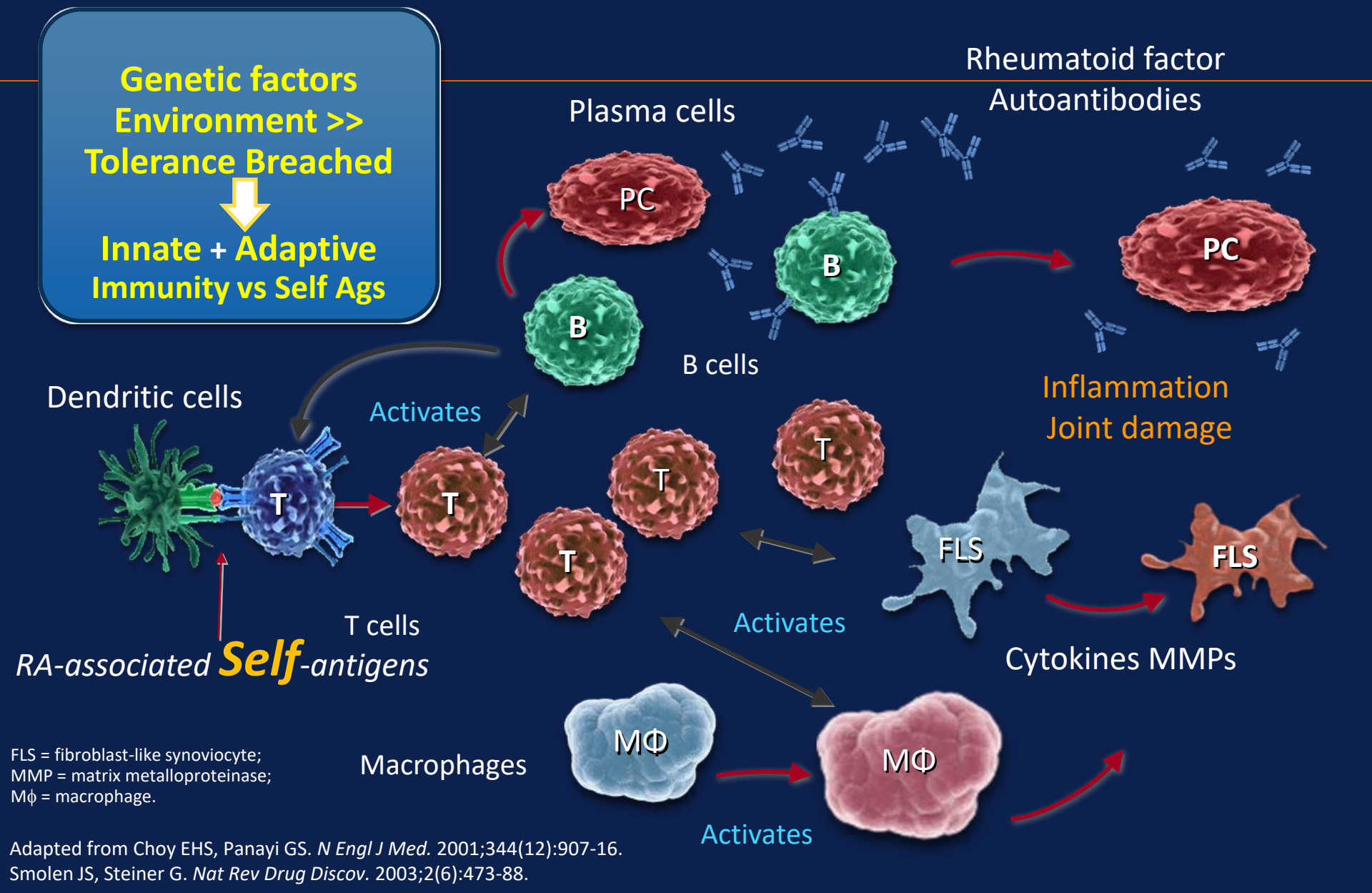
Protein now larger and differently charged

Shared Epitope

- Part of the MHC class II molecule binding site
- Patients with the shared epitope have a binding site able to accommodate citrullinated self-antigens



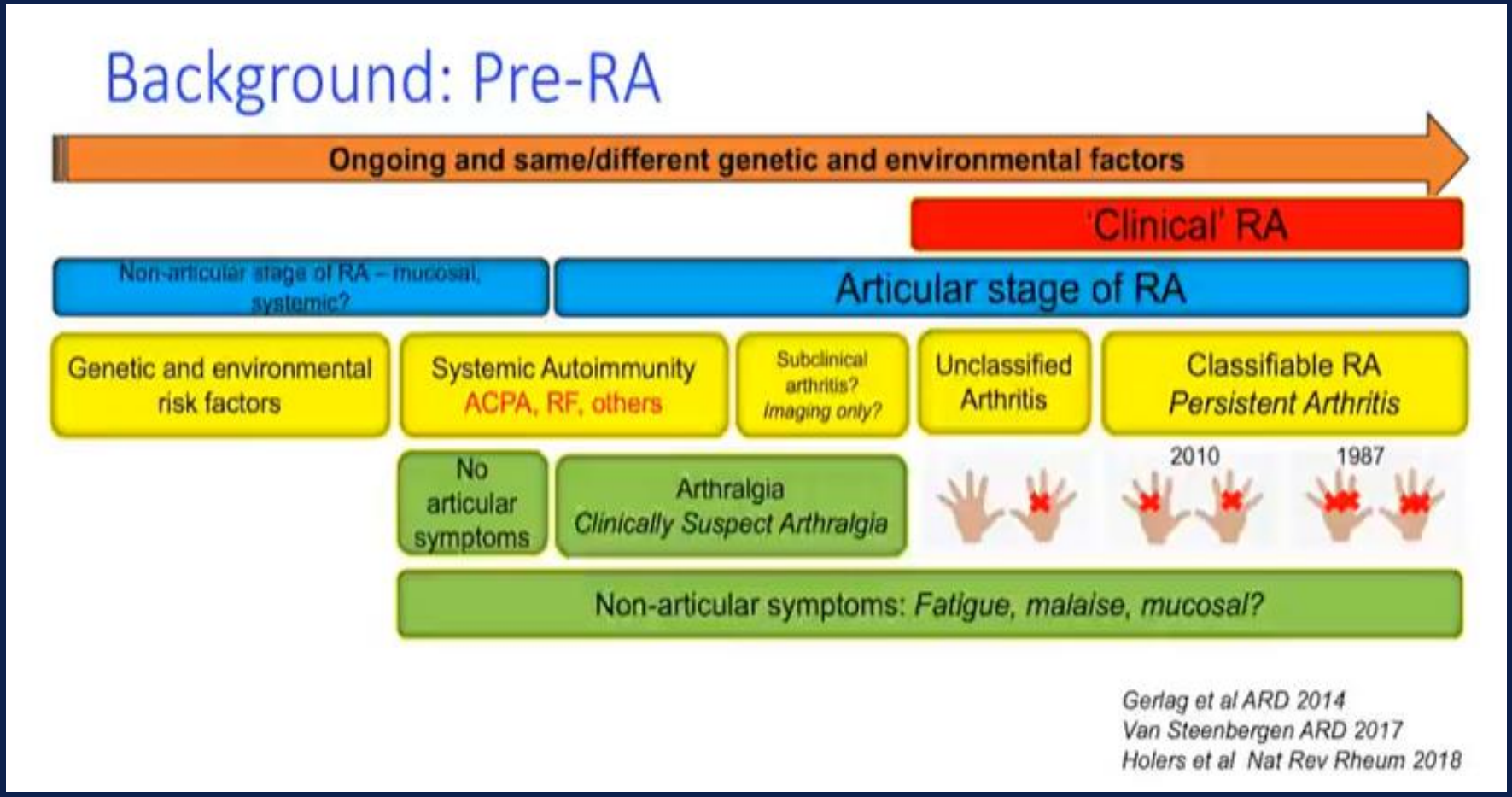
Etiopathogenesis of Rheumatoid Arthritis



FLS = fibroblast-like synoviocyte;
MMP = matrix metalloproteinase;
Mϕ = macrophage.

Adapted from Choy EHS, Panayi GS. *N Engl J Med.* 2001;344(12):907-16.
Smolen JS, Steiner G. *Nat Rev Drug Discov.* 2003;2(6):473-88.

Preclinical Rheumatoid Arthritis



RA-related autoimmunity and inflammation present long before onset of intra-articular inflammation=preclinical RA

RA-related autoantibodies detectable 3-5 years before clinically detectable RA

- Increased prevalence and increased titers over time
- IgG isotype imparts higher risk of future RA
- Expanded number of antigenic targets over time
- Dual positivity for RF and ACPA provides stronger prediction for future RA

Levels of cytokines and chemokines elevated, increasing as patient gets closer to RA

Multiple studies in RA suggest that autoimmunity in RA originates outside the joints—likely a mucosal site

- Lungs
- Periodontal surfaces
- GI tract

RA begins with systemic autoimmunity and inflammation (perhaps originating in the lungs) and spreads to the joints.

Deane and Holers, Clin Ther 2019

What % of Asymptomatic ACPA Positive People Develop RA?

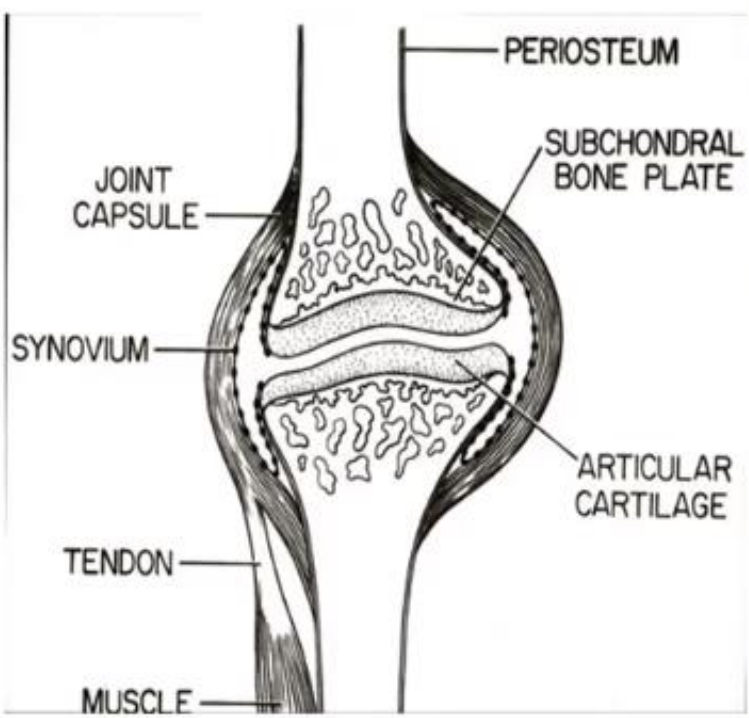
- Swedish twin cohort (n=12,590) born before 1959
- 350/12,590 were anti-CCP (ACPA) positive=2.78%
- 103/350 had RA at time of blood donation (29.4%)
- 21 of remaining 247 developed RA over 3 years (<3%/year)

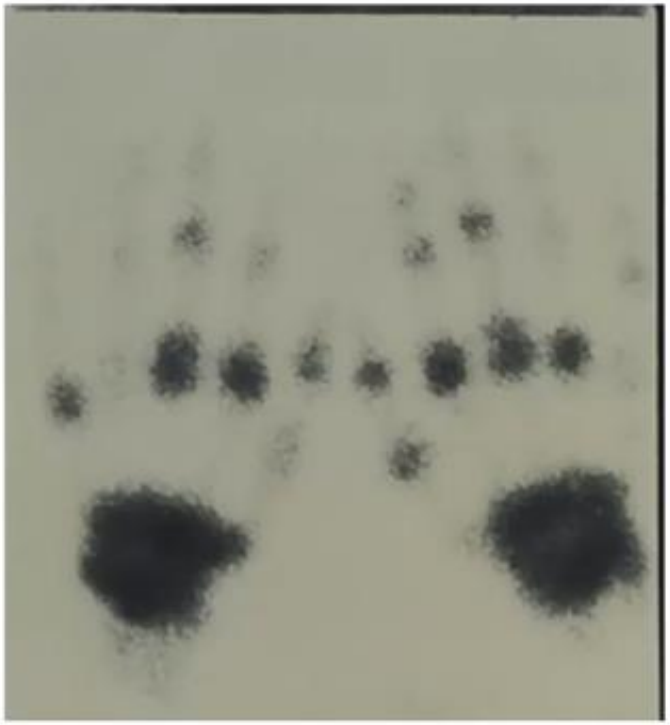
- Increasing numbers of ACPA reactivities increased risk of imminent RA
- Higher ACPA titers also associated with a higher risk of RA

Hensvold AH et al Ann Rheum Dis 2017

How does RA transition from a systemic disease to an articular one?

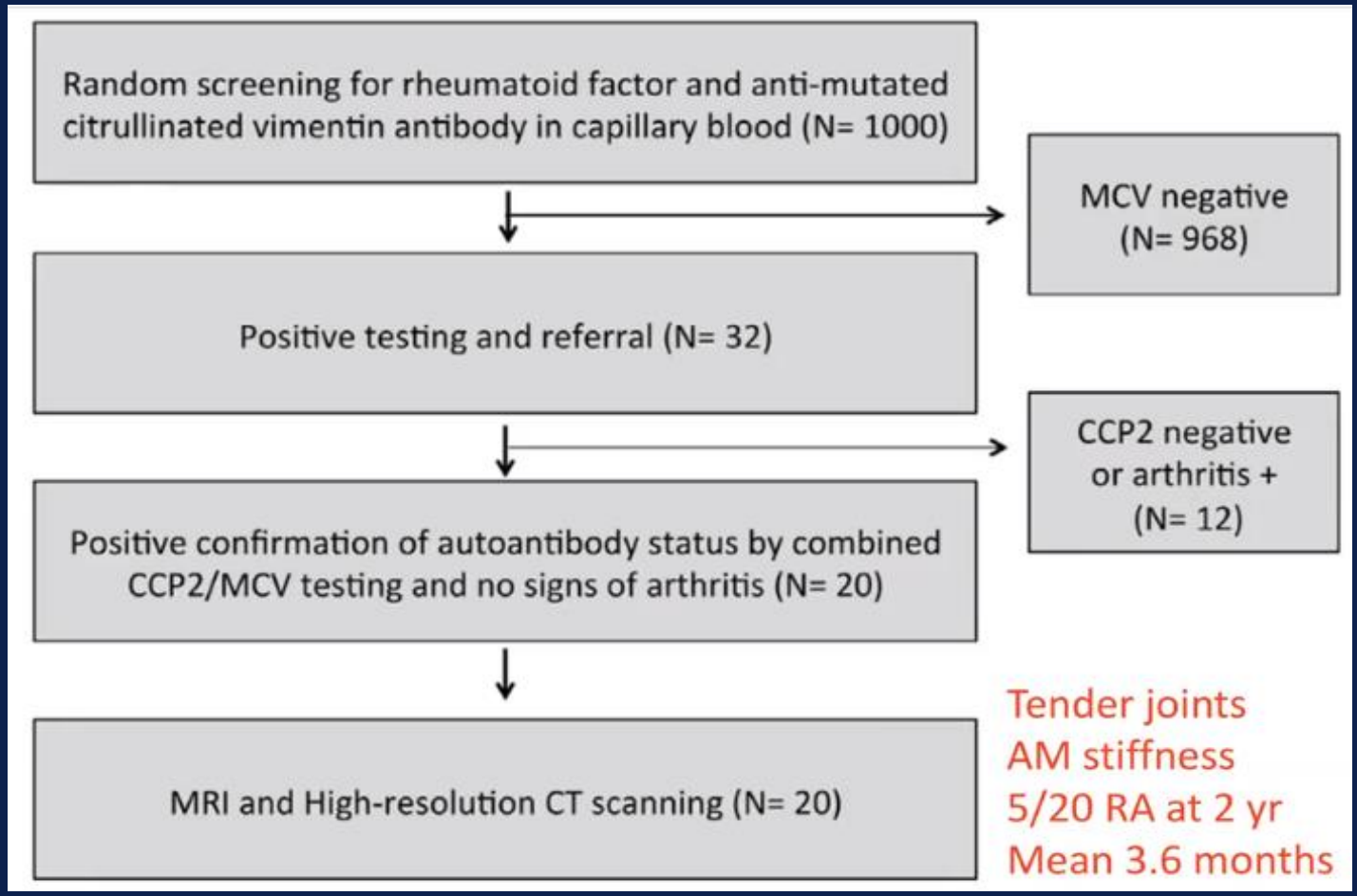
How does RA get into the synovial joint?





1. ACPA immune complexes in situ incite inflammation
2. Bone Marrow Process—vascular channels
3. Entheseal/Tendinous origin

When and how does inflammation start in RA? Which anatomical structures initially involved in preclinical RA?

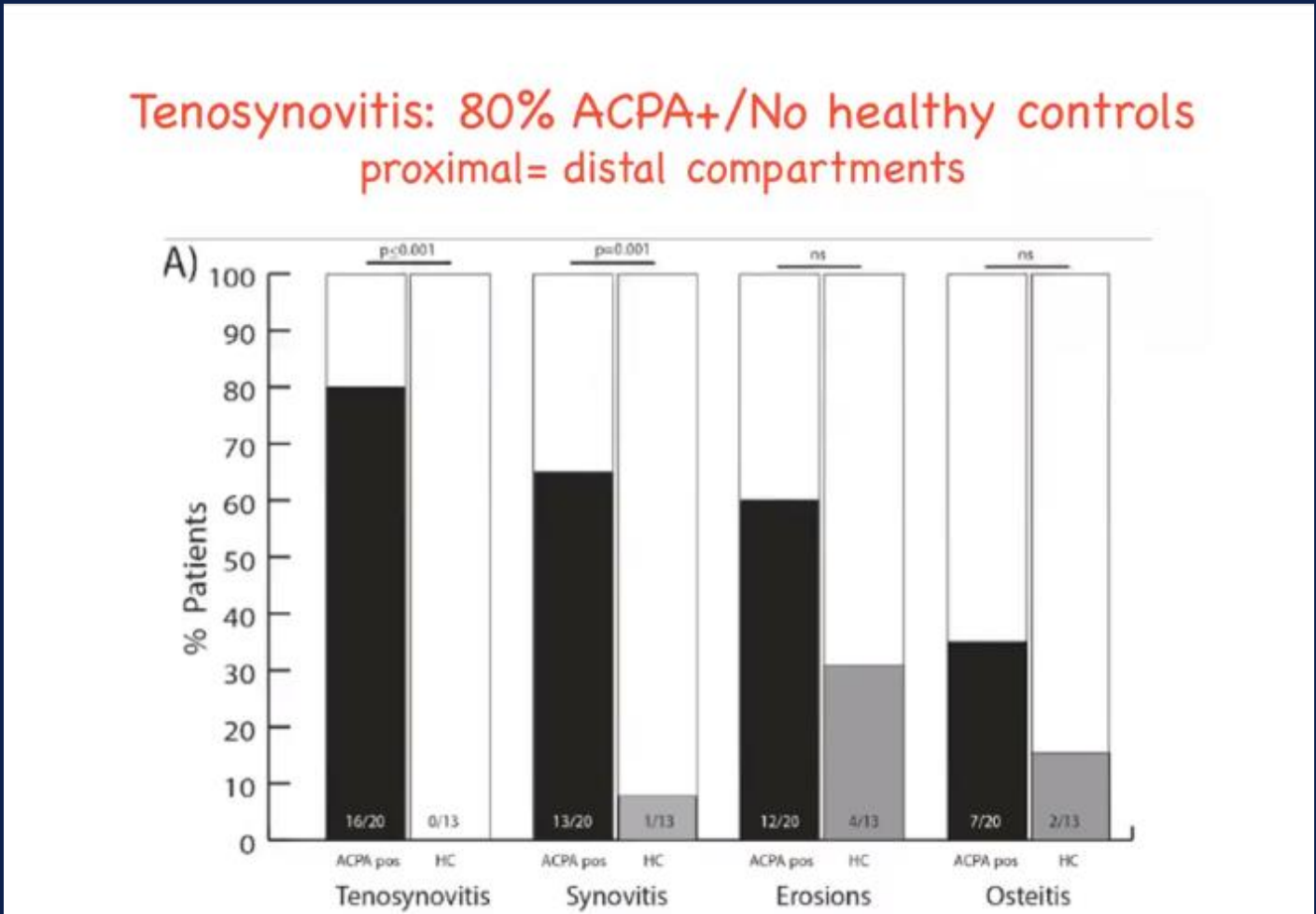


20 ACPA + individuals at risk for RA underwent MRI and HRCT

Kleyer in Seminars Arth Rheum 2016

RESULTS

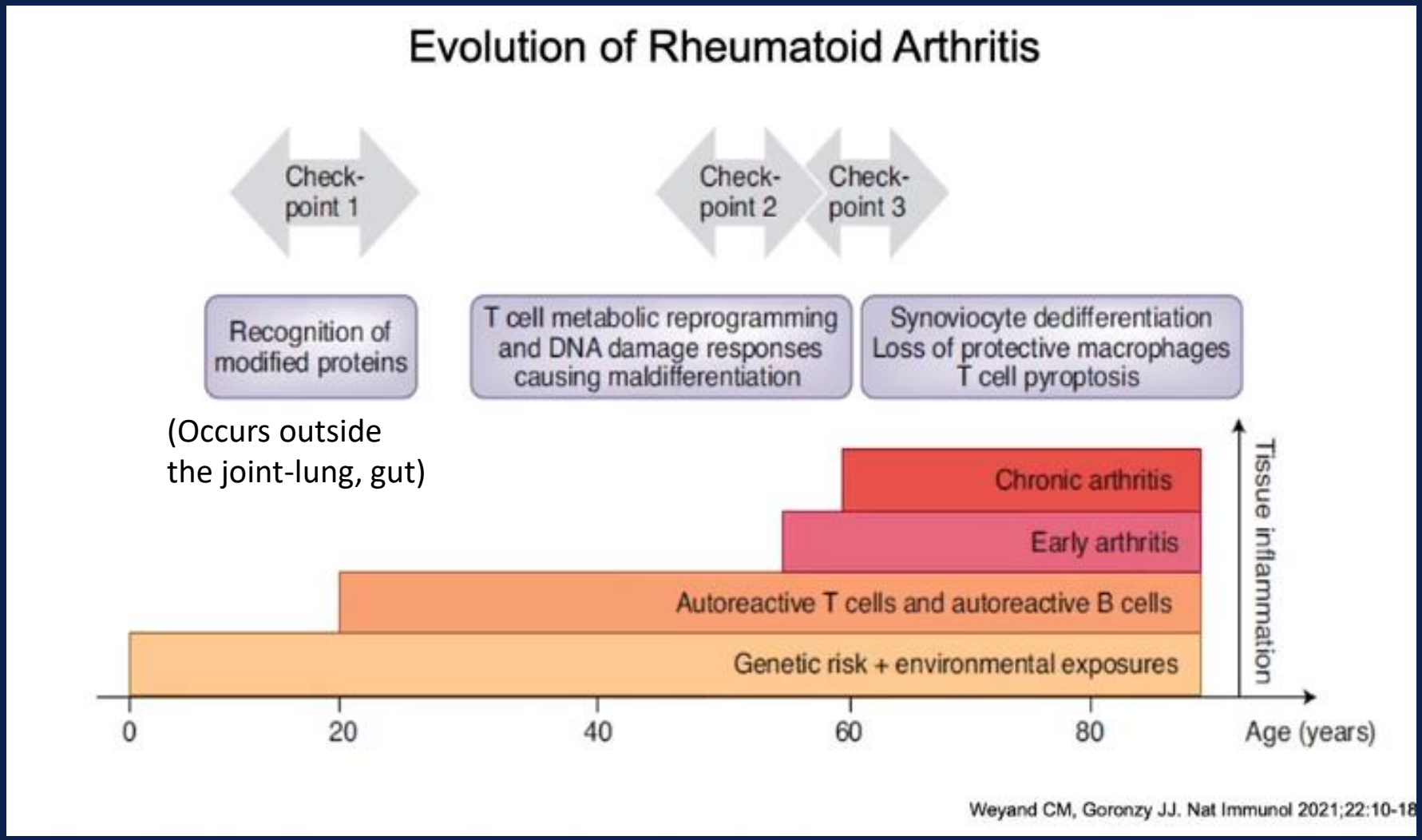
Substantial tenosynovial inflammation in ACPA + individuals at risk to develop RA



Kleyer in Seminars Arth Rheum 2016

Evolution of RA-almost lifelong process

1) Tolerance breakdown (peripheral tolerance defect). Asymptomatic autoimmunity.
2)Innate and adaptive immune cells enter the synovial membrane.
3) Acute synovitis transitions to chronic, destructive synovitis.



Should we treat patients with pre-clinical RA?

Background: Placebo-controlled clinical trials in 'pre-RA'

DUTCH DEX: dexamethasone, no prevention *Bos et al Ann Rheum Dis 2010*

PRAIRI: rituximab/steroids, delay no prevention *Gerlag et al Ann Rheum Dis 2019*

STAPRA: atorvastatin, no prevention *van Boheemen et al RMD Open 2021*

TREAT EARLIER: methotrexate/steroids, no prevention but improved symptoms and disease activity *Krijbolder et al Lancet 2022*

APIPPRA: abatacept (ongoing) *Al-Laith et al Trials 2019*

ARIAA: abatacept (ongoing, early reports of delay and possible prevention) *Rech et al ACR 2022 Abstract 0530*

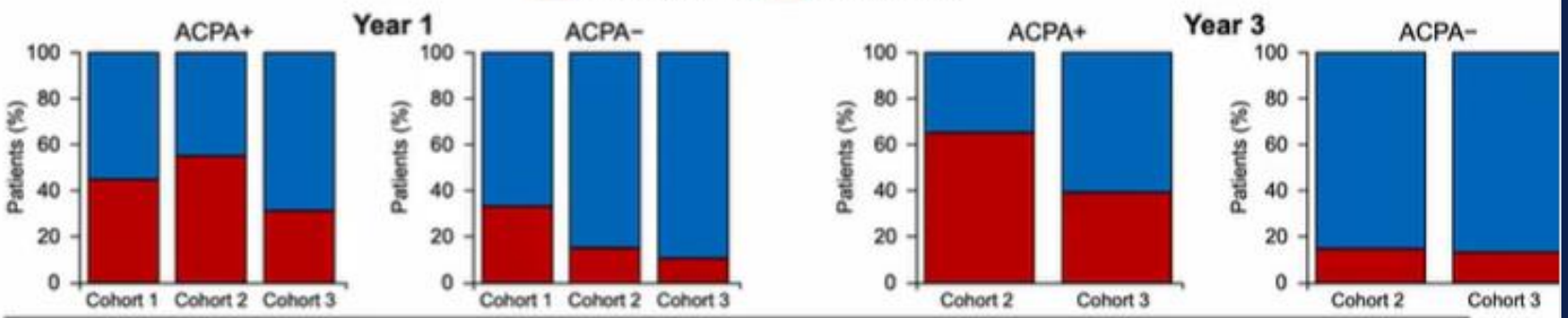
Probably Not

Arthralgia patients with subclinical synovitis demonstrated using ultrasound or MRI

How often does subclinical synovitis result in clinical inflammatory arthritis?

- Subclinical synovitis in hands or feet of arthralgia patients visualized using
  - Ultrasound (2 cohorts, n=166/162): subclinical synovitis = grayscale ≥2 and/or power Doppler ≥1
  - MRI (1 cohort, n=473): subclinical synovitis = synovitis score ≥1 by 2 readers
- Patients were assessed prospectively for 1 year for development of clinical inflammatory arthritis (IA), stratified by ACPA status
- In Cohorts 1, 2, and 3, subclinical synovitis was found in 36%, 41%, and 31% at presentation, and in 22%, 15%, and 18% at 1 year

Progression to IA in patients with subclinical synovitis by ACPA status



Most ACPA− patients with subclinical synovitis do not develop inflammatory arthritis.
Subclinical synovitis should not be used for initiating early treatment in this population

Rogier et al. ACR 2020 #481

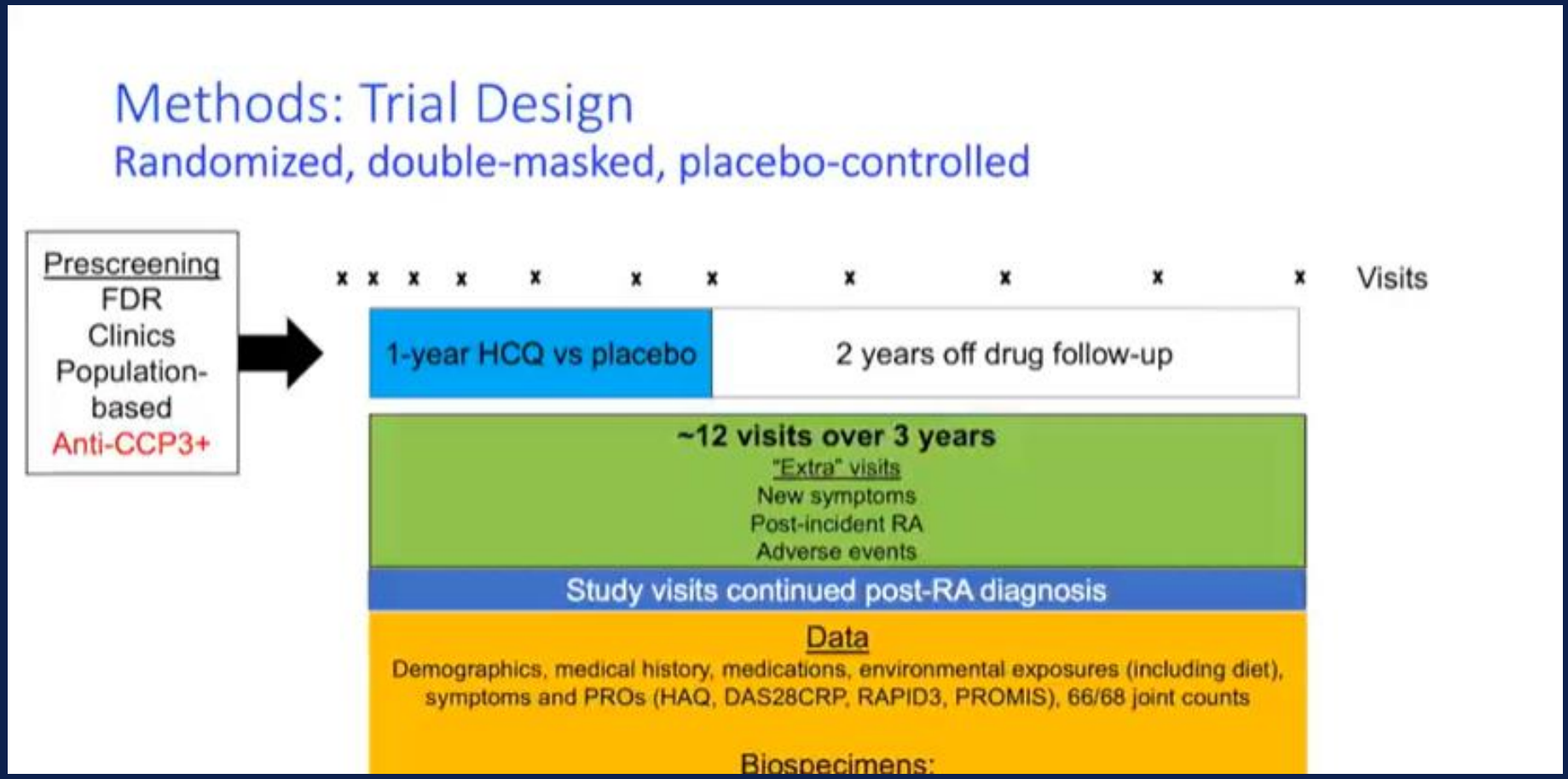
StopRA Trial

Hydroxychloroquine Does Not Prevent the Future Development of Rheumatoid Arthritis in a Population with Baseline High Levels of Antibodies to Citrullinated Protein Antigens and Absence of Inflammatory Arthritis:
Interim Analysis of the StopRA Trial

ACR Convergence 2022 Abstract 1604

Presenter: Kevin D. Deane, MD/PhD University of Colorado Anschutz Medical Campus

Trial Design



Primary Endpoint

Methods: Primary Endpoint

Development of clinically-apparent RA by 36 months

Clinically-apparent RA defined as:

≥1 swollen joint on physical examination consistent with RA-like synovitis and:

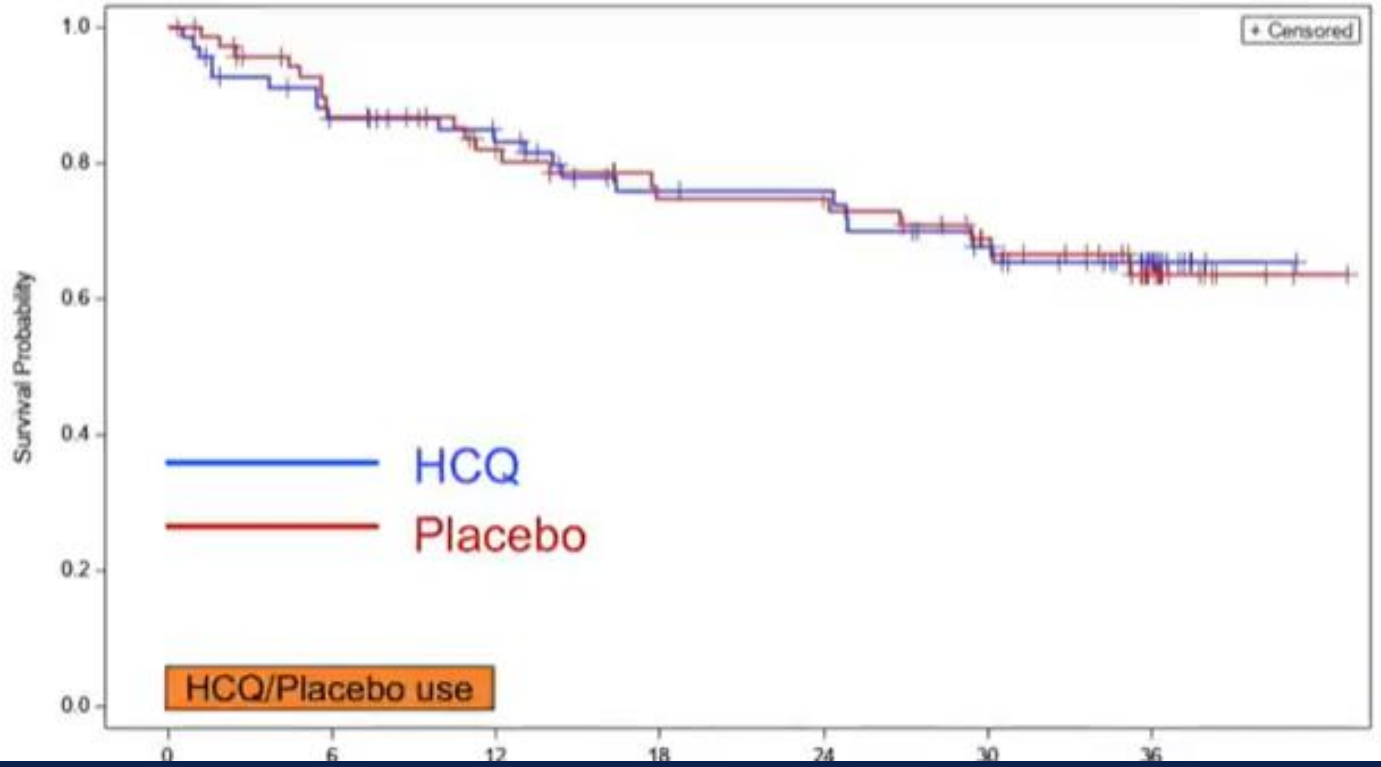
RA classified per 2010 ACR/EULAR criteria (score ≥6)

OR

≥1 erosion identified via x-ray of the hands, wrists, and feet

Results

Survival estimates of the rates of development of incident clinically-apparent RA (mITT n=73 placebo, 69 HCQ)



Development of RA was similar for each arm:

HCQ: 34%
Placebo: 36%
p=0.844

No difference during HCQ use, or after

Conclusion

Conclusions

From interim results from the StopRA trial:

In individuals who are anti-CCP3(+) >=2 ULN without IA at baseline, 1 year of HCQ is not superior to placebo in preventing or delaying the development of classified RA at 3 years

The study was halted due to futility

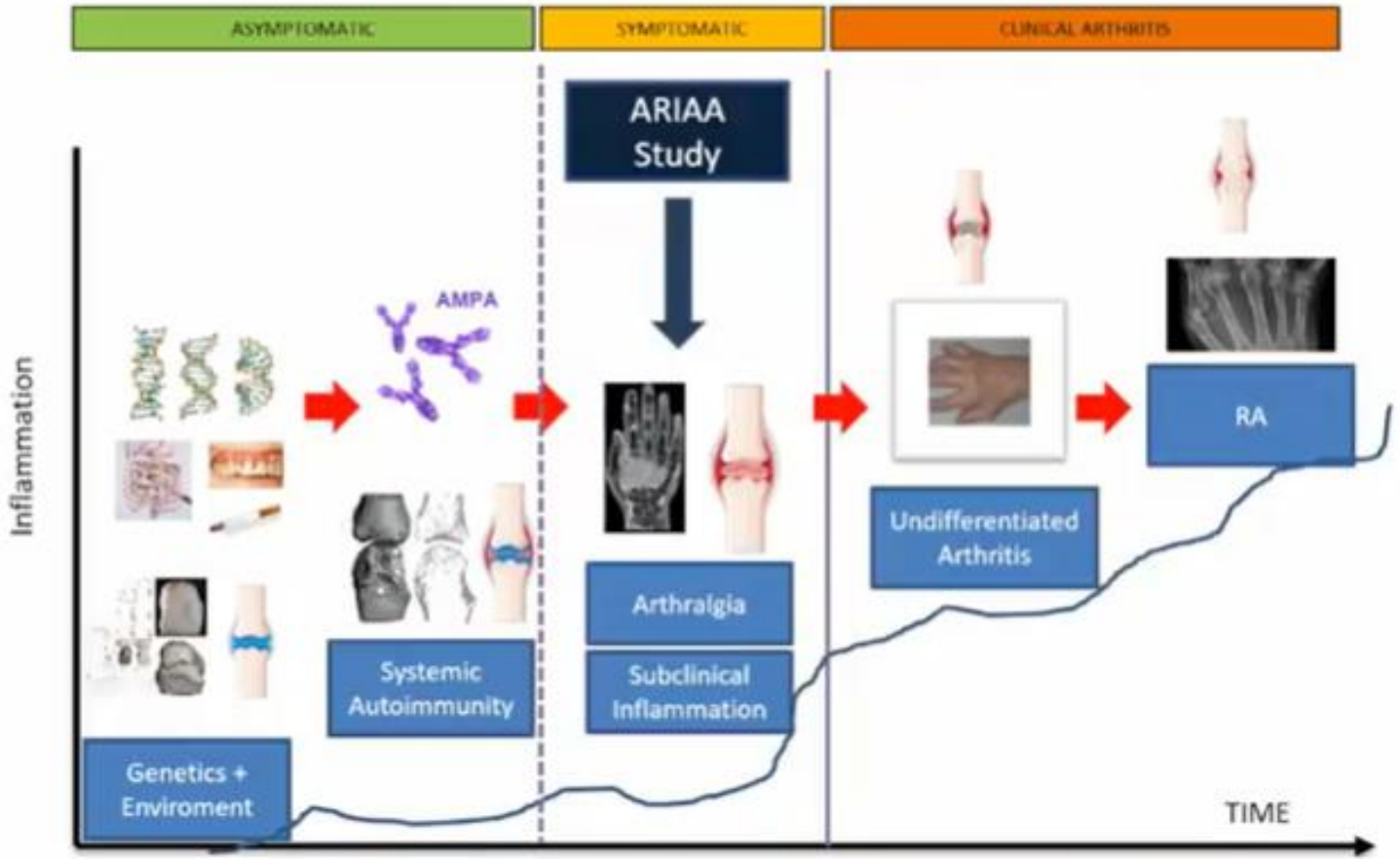
Abatacept reverses subclinical arthritis in patients with high-risk to develop rheumatoid arthritis -results from the placebo-controlled randomized controlled ARIAA study in RA-at risk patients

The ARIAA-study

J. Rech; M. Ostergaard; M. Hagen; L. Mendez; K. Tascilar; A. Kleyer; G. Kroenke; V. Schoenau; S. Kleinert; X. Baraliakos; M. Fleck; A. Rubbert-Roth; F. Behrens; M. Feuchtenberger; M. Zaenker; R. Voll; C. Glaser; E. Feist; G. Burmester; K. Karberg, J. Strunk; J. D. Cañete Crespillo; L. Sanolt, E. Naredo; G. Schett

Abstract Number: 0455

Phases in the development of RA

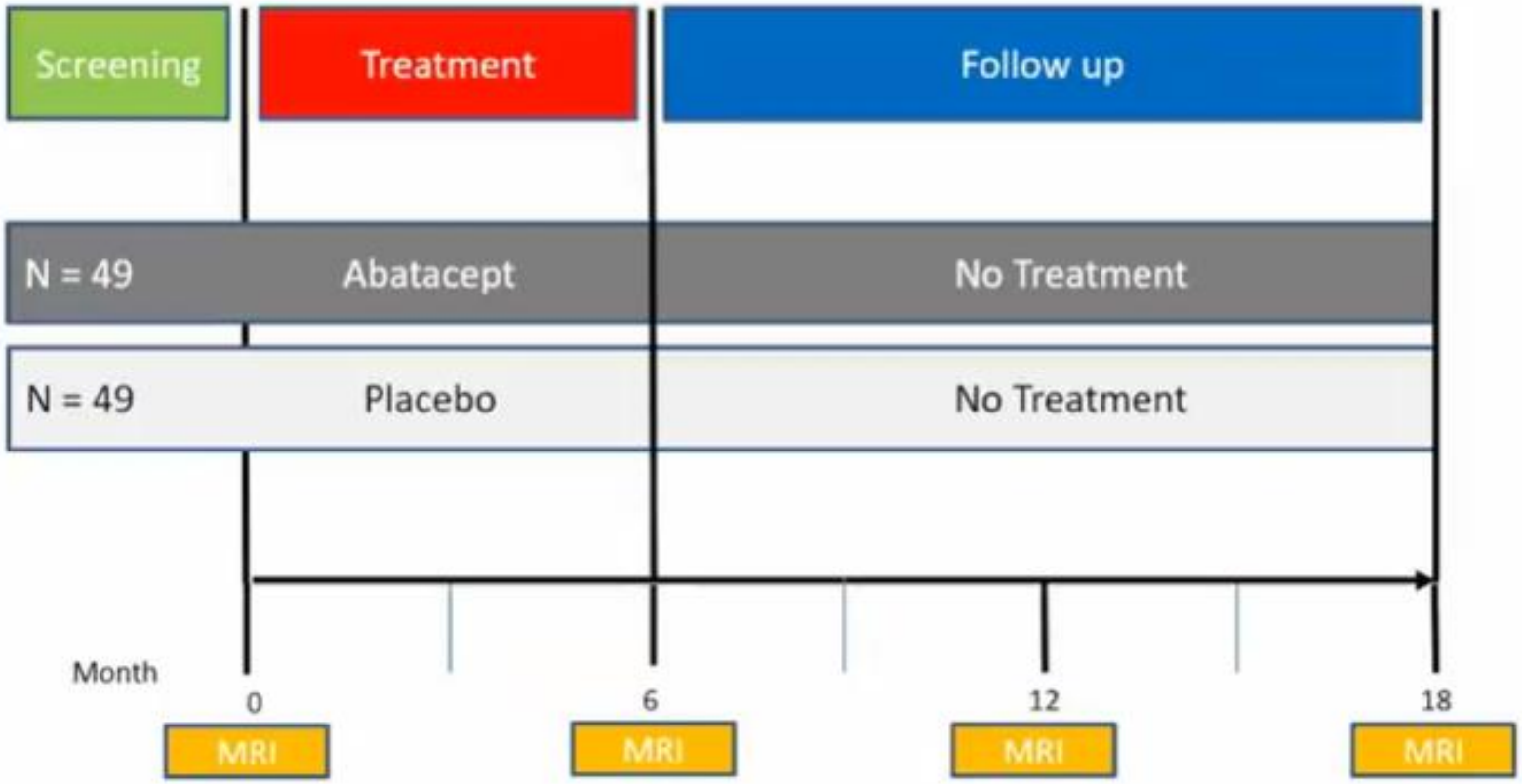


Study Design

Abstract Number: 0455

Study design

Randomized double-blinded placebo controlled study in RA at risk patients.



Patients

Abstract Number: 0455

Main Inclusion and Exclusion Criteria

Females and males aged ≥ 18 years at time of consent

ACPA
positivity
(with or without RF)

Arthralgia
present for at least 6 weeks prior to inclusion or in the past history

MRI
inflammation (synovitis, tenosynovitis or osteitis) **in the dominant hand**

No present or past signs of swelling

No glucocorticoid or DMARD treatment

Endpoints

Abstract Number: 0455

Key Endpoints

Primary endpoint

Improvement in at least one of the **MRI inflammation** parameters (any change from baseline > 0 assessing synovitis, tenosynovitis and osteitis) according to the RAMRIS score

Key secondary endpoint

Progression to arthritis as evident by clinical joint swelling

Primary Endpoint

Abstract Number: 0455

Primary Endpoint

ITT Analysis

Improvement in MRI Inflammation Score		Abatacept	Placebo	Total
NO	N (%)	19 (38.8)	34 (69.4)	53 (54.1)
YES	N (%)	30 (61.2)	15 (30.6)	45 (45.9)
				P = 0.0043

Improvement (> 0 points) of MRI synovitis, tensynovitis or osteitis between baseline and 6 months follow-up based on central blinded reading

Secondary Endpoints

Abstract Number: 0455

Termination or progression to arthritis

		Abatacept	Placebo	Z Total
Early Termination				
NO	N (%)	42 (85.7)	28 (57.1)	70 (71.4)
YES	N (%)	7 (14.3)	21 (42.9)	28 (28.6)
				P= 0.0032
Progression to Arthritis				
NO	N (%)	45 (91.8)	32 (65.3)	77 (78.6)
YES	N (%)	4 (8.2)	17 (34.7)	21 (21.4)
				P=0.0025

Conclusions

Abstract Number: 0455

Conclusions

- Abatacept is superior to placebo in **improving subclinical inflammation** in RA at-risk patients (ACPA+, MRI+, Arthralgia+) at 6 months
- Abatacept is superior to placebo in **inhibiting the progression to arthritis** at 6 months
- Use of abatacept in RA at-risk patients is safe and **no new safety issue** emerged
- Follow-up results at 18 months will reveal whether the effect of a time-limited intervention of abatacept has a **sustained effect** on inhibition of progression to arthritis

Effect was maintained at 18 months

TREAT EARLIER Study

- Should one use DMARD therapy in a seropositive patient with arthralgias before clinically evident synovitis in an effort to avoid or delay the development or damage of RA?
- MTX initiated in arthralgia patients did not prevent the development of inflammatory arthritis.

  arthralgias > 12 weeks

  seropositive

  MRI-detected subclinical joint inflammation
- MTX did appear the modify the disease course as shown by serial MRI.

  Other endpoints better with MTX: HAQ-DI, Pain, AM stiffness, Presenteeism

  Perhaps less severe disease, at least in the short term

https://www.thelancet.com/journals, 2022

Targeted Therapies

- Treatments for rheumatoid arthritis (RA) prior to 1998 were discovered fortuitously, even MTX.
- Now, due to a greatly improved understanding of the immunopathogenesis of the disease, we have developed targeted therapies.

Targeted Therapies

- However, which treatment is best for the patient in front of you?
- Fail 1 drug-allows for further disease progression, possible unnecessary side effects, and costs $30-40,000.
- How can we best maximize the likelihood of a therapeutic success?

Treatment Targets—T cells, B cells, Cytokines, and Signalling Pathways Involved in RA

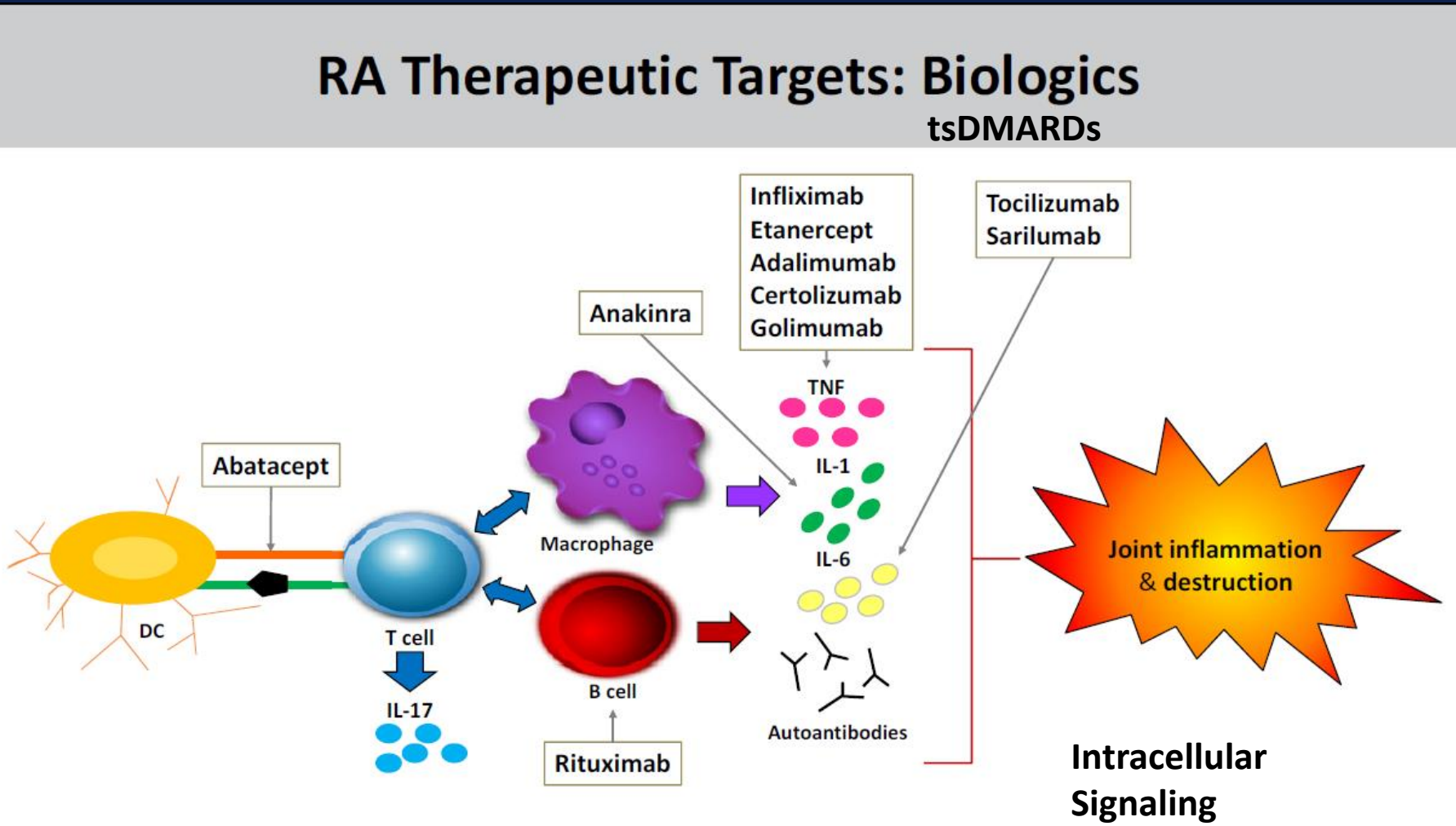


Image adapted from Koenders MI, van den Berg WB. *Trends Pharmacol Sci*. 2015;36(4):189–195.

Need a biomarker(s) to predict response to treatment—*None available*

Need for Biomarkers in RA[1-4]

Mechanisms responsible for variable response to therapy are still unknown, and there are no biomarkers in regular clinical use that are predictive of treatment response to individual therapeutic agents

The result is a "trial and error" approach to the management of RA

- The most recent ACR and EULAR recommendations support the use of any of the available targeted therapeutics following failure on conventional synthetic csDMARDs
- Patients are exposed to a therapeutic lottery of drugs, which may be ineffective and cause unnecessary adverse events
- Try to identify biomarkers of treatment response in diseased tissue, as the search in peripheral blood has been largely unsuccessful

1. Cuppen BVJ et al. *Rheumatology (Oxford)*. 2016;55:826-839. 2. Fraenkel L et al. *Arthritis Care Res (Hoboken)*. 2021;73:924-939.
3. Smolen JS et al. *Ann Rheum Dis*. 2020;79:685-699. 4. Pitzalis C et al. *Curr Opin Rheumatol*. 2013;25:334-344.

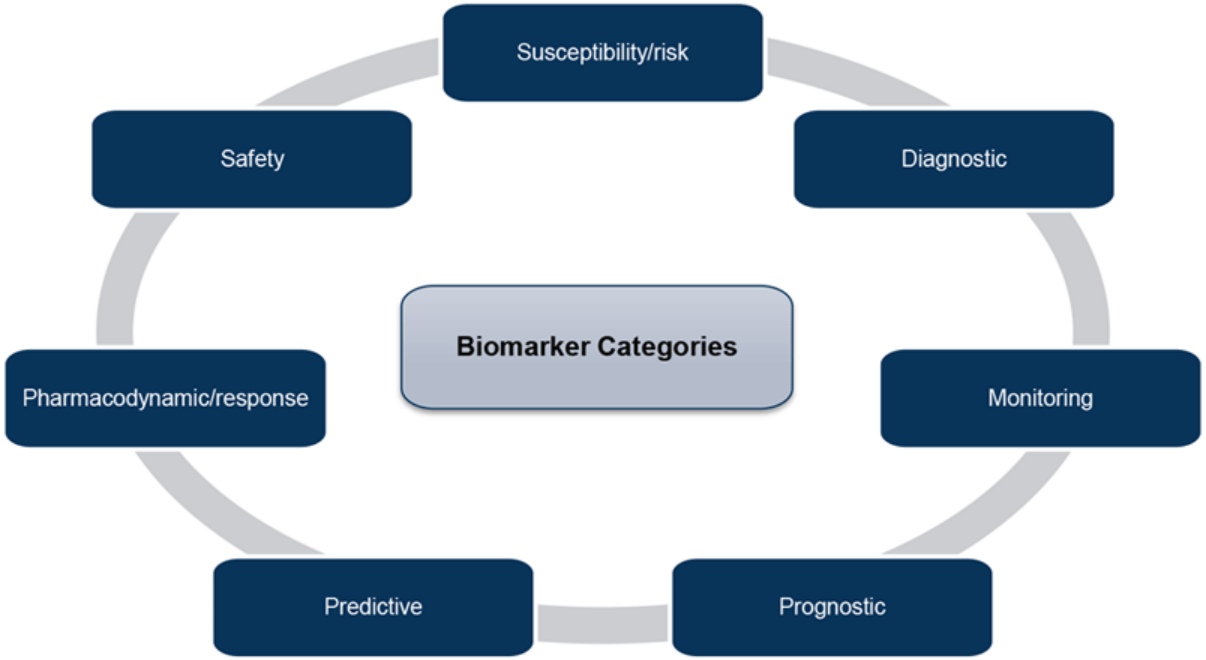
PeerView.com

What Is a Biomarker?[1]

- The Biomarkers, EndpointS, and other Tools (BEST) glossary defines a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions"
- Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers
- A biomarker is not an assessment of how an individual feels, functions, or survives

1. https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification#:~:text=Transcript,or%20intervention%2C%20including%20therapeutic%20interventions.

Biomarker Categories: BEST Glossary[1]



1. https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification#:~:text=Transcript,or%20intervention%2C%20including%20therapeutic%20interventions.

PeerView.com

Overview of Biomarkers as an Aid in Diagnosis, Prognosis, and Monitoring of RA[1]

Biomarker	Comments	Clinical Adoption	IVD Products
ACPA (anti-CCP)	• Most important marker in RA	Wide	Yes
RF	• Classical RF (total, but mostly IgM) used on clinical chemistry analyzer	Wide	Yes
ACPA (anti-CCP) – isotypes	• IgA present in early RA; quite specific for RA • IgM not very specific • IgA used in CCP3.1 and separate in some assays	Moderate (geography dependent)	Yes
14–3-3η (eta)	• High sensitivity, low specificity	Moderate (geography dependent)	Yes
Circulating calprotectin	• Marker for neutrophil-mediated inflammation	Moderate (geography dependent)	(Yes)
Vectra DA	• Multi-parameter marker for disease activity	Moderate (geography dependent)	No (only LDT)
RF isotypes	• Individual isotypes available on many platforms; value beyond diagnosis	Moderate (geography dependent)	Yes
Anti-Ra33	• Known for long time • Associated with mild form of RA • Recent focus on IgM and IgA	Limited	Yes
Anti-PAD4, anti-PAD3/4	• Recently established • Associated with severe form of RA	Limited	No
Anti-CarP	• Not specific for RA, but useful in combination with ACPA/RF • Associated with erosive disease	Limited	No (only LDT)

1. Mahler M et al. *Autoimmun Rev*. 2020;19:102506.

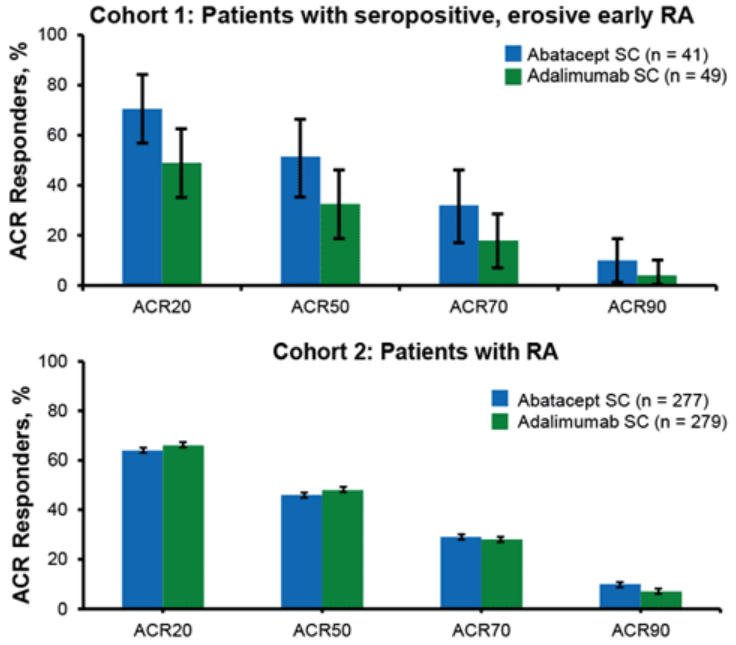
PeerView.com

ACPA and RF=diagnostic and prognostic of disease severity

In vitro diagnostic Products

Efficacy of Abatacept and Adalimumab in Patients With Early RA With Multiple Poor Prognostic Factors: Post Hoc Analysis of AMPLE[1]

- **Cohort 1:** patients with ≤6 months' disease duration who were seropositive for RF and/or ACPA and had >1 radiographic erosion
- **Cohort 2:** patients with RA who did not meet poor prognostic criteria
- Trend toward improved disease activity and physical function with abatacept versus adalimumab in patients with early RA and poor prognostic factors



1. Fleischmann R et al. *Rheumatol Ther*. 2019;6:559-571.

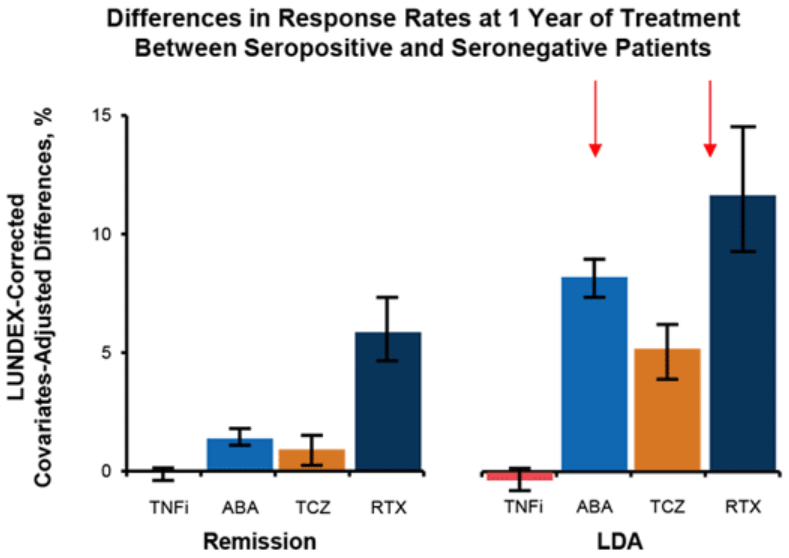
PeerView.com

PeerView.com/PPX910

Early RA patients with poor prognostic factors (RF, ACPA, 1 erosion) did better with Abatacept

Seropositivity Shown to Be Associated With Increased Effectiveness of Non–TNF Inhibitors, Especially Rituximab and Abatacept[1]

- Data from 27,583 patients treated with biologic antirheumatic agents were pooled from 16 registries
- Seropositivity was associated with longer drug retention and decreased disease activity for rituximab and abatacept
- Slight associations between seropositivity and effectiveness for tocilizumab and none for TNF inhibitors



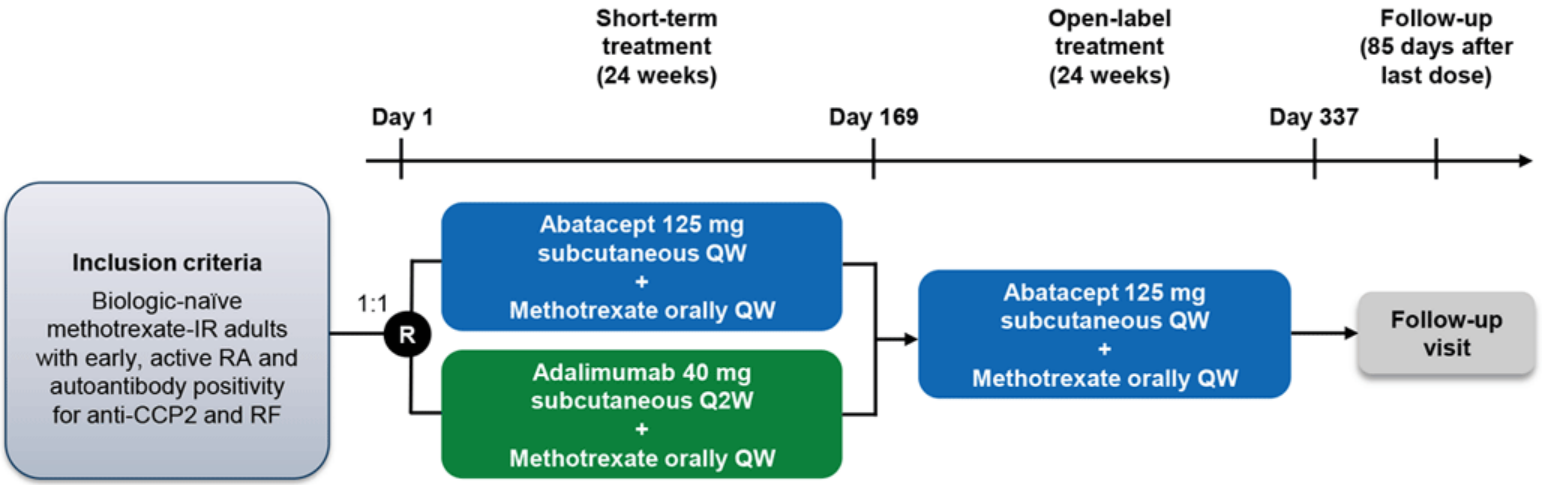
1. Courvoisier DS et al. *Rheumatology (Oxford)*. 2021;60:820-828.

PeerView.com

PeerView.com/PPX910

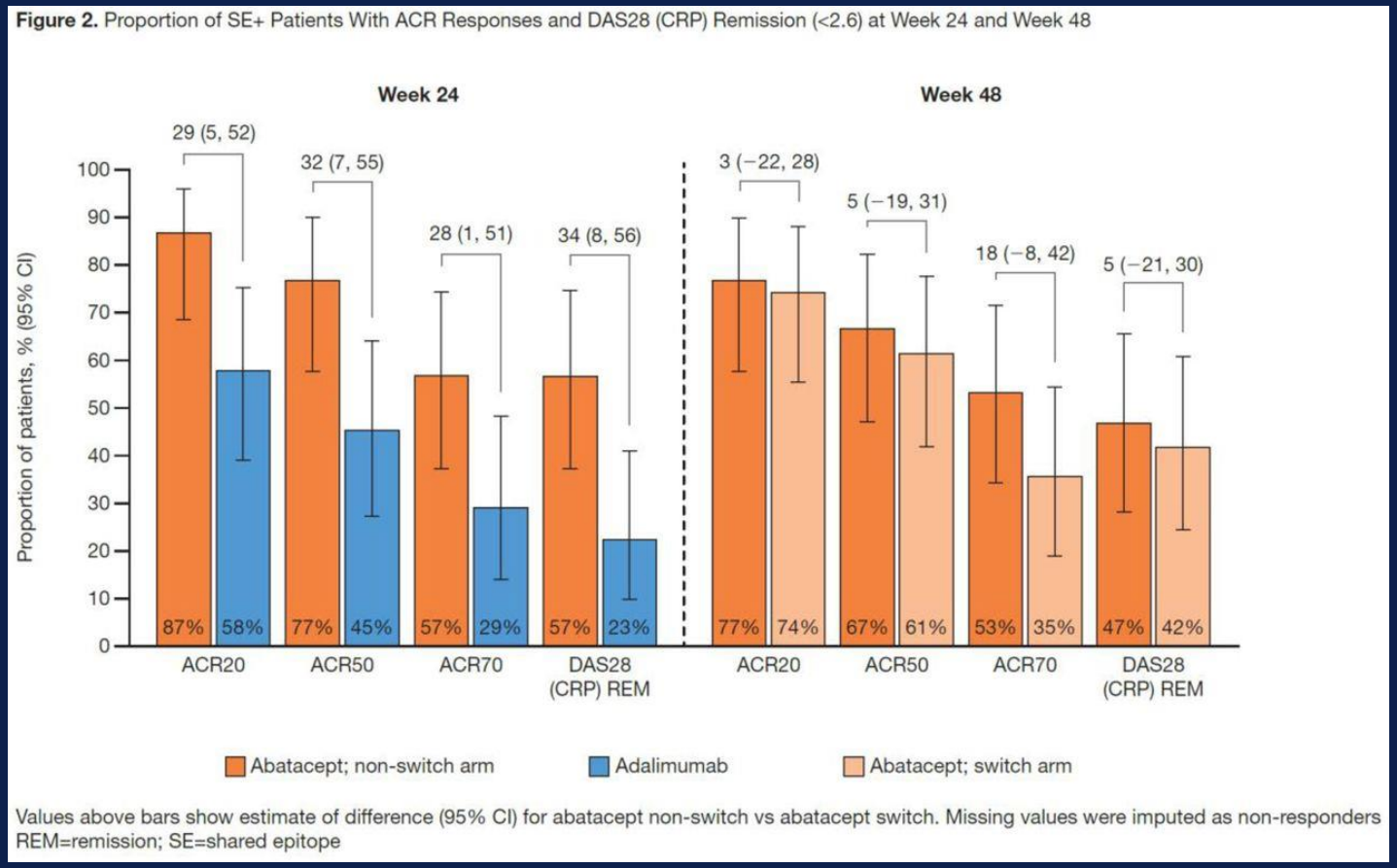
Seropositive and seronegative patients do not respond the same to non-TNF inhibitors—abatacept, rituximab, tocilizumab.

Early AMPLE: A Head-to-Head, Randomized, Single-Blind Study in Autoantibody-Positive Early RA[1]



1. Rigby W et al. *Arthritis Res Ther.* 2021;23:245.

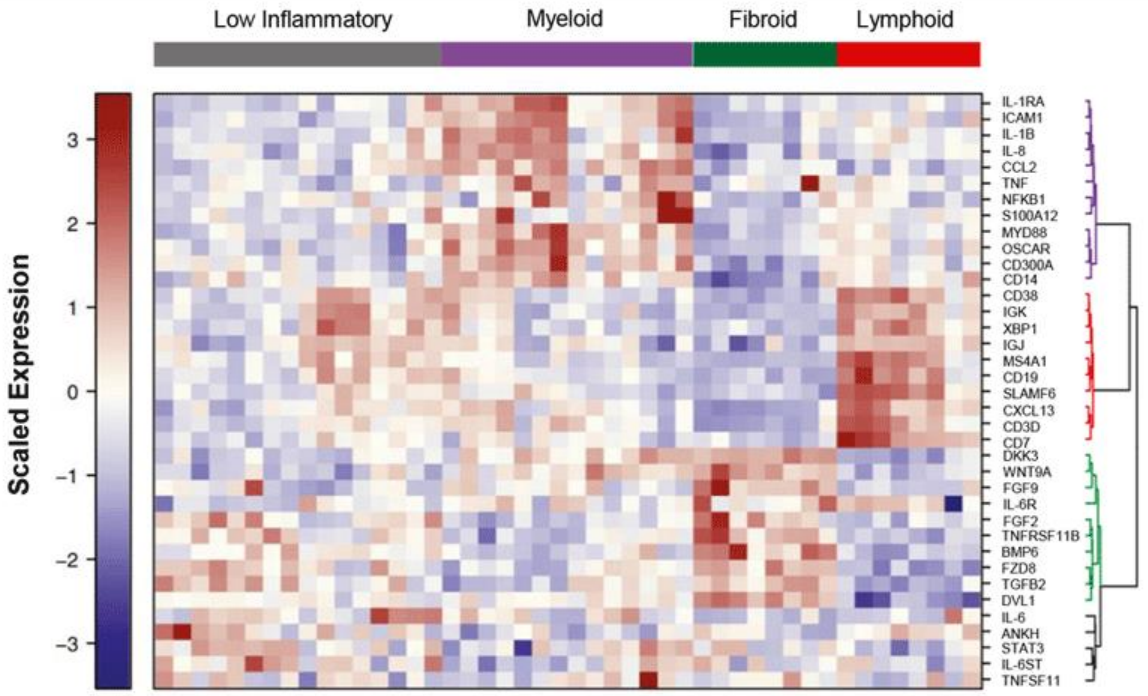
Early RA, Dual Seropositive, HLA-DRB1positive EULAR 2020



Seropositive patients respond differently to abatacept and adalimumab, with more pronounced differences in SE-positive patients.

Biologic processes that we call “RA” not the same between patients (established RA patients here)

Evidence for Four Major Phenotypes of RA Synovium, Each With Distinct Underlying Gene Expression Signatures[1]



1. Dennis G et al. *Arthritis Res Ther*. 2014;16:R90.

PeerView.com

PeerView.com/PPX910

Synovial biopsy>>4 pathotypes

Different genes associated with different pathotypes

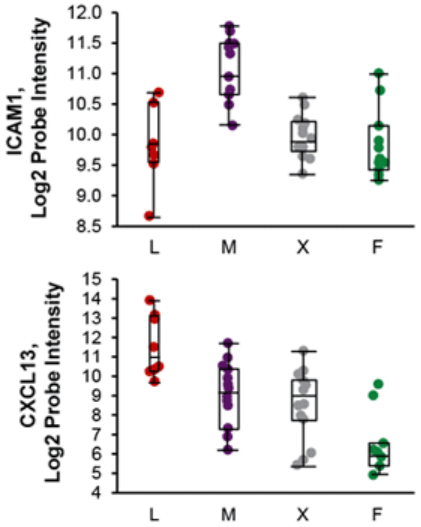
Lymphoid=B and T cells
Fibroid=acellular

Myeloid=neutrophils and monocytes
Low inflammatory=few cells

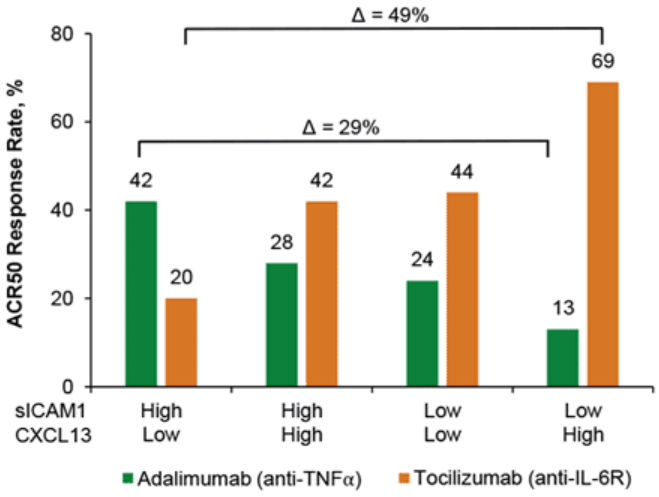
Synovial Phenotypes in RA Correlate With Response to Biologic Therapeutics[1]

Predict with blood test

ICAM1 and CXCL13 Genes Are Expressed at Highest Levels in the Myeloid (M) and Lymphoid (L) Phenotypes, Respectively



Lymphoid (CXCL13) and Myeloid (sICAM1) Serum Biomarkers Define RA Patient Subgroups With Differential Clinical Response to Anti-TNFα Compared With Anti-IL-6R in ADACTA



1. Dennis G et al. *Arthritis Res Ther*. 2014;16:R90.

PeerView.com

PeerView.com/PPX910

Myeloid pathotype (serum ICAM1) responds better to anti-TNF
Lymphoid pathotype (serum CXCL13) responds better to anti-IL6R

Synovial Cellular and Molecular Signatures Stratify Clinical Response to csDMARD Therapy and Predict Radiographic Progression in Early RA[1]

- 144 consecutive treatment-naïve, early RA patients (symptom duration <12 months) underwent US-guided synovial biopsy before and 6 months after DMARD initiation
- Synovial biopsies were analyzed for cellular (immunohistology) and molecular (NanoString) characteristics and results compared with clinical/imaging outcomes

Three Specific Pathology Subgroups Identified in Early, Treatment-Naïve RA Patients

Lympho-myeloid	Diffuse-myeloid	Pauci-immune-fibroid
Dominated by the presence of B cells in addition to myeloid cells	Myeloid lineage predominance but poor in B cells	Characterized by a paucity of immune cells and a prevalence of stromal cells

- Elevation of myeloid- and lymphoid-associated gene expression is strongly correlated with disease activity, acute phase reactants, and DMARD response at 6 months
- Elevation of synovial lymphoid-associated genes is correlated with autoantibody positivity and elevation of osteoclast-targeting genes predicting radiographic joint damage progression at 12 months
- Patients with predominant pauci-immune pathology showed less severe disease activity and radiographic progression

1. Humby F et al. *Ann Rheum Dis*. 2019;78:761-772.

Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial

Felice Rivellese[1,2,39], Anna E. A. Surace[1,2,39], Katriona Goldmann[1,2], Elisabetta Sciacca[1,2], Cankut Çubuk[1,2], Giovanni Giorli[1,2], Christopher R. John[1,2,40], Alessandra Nerviani[1], Liliane Fossati-Jimack[1], Georgina Thorborn[1], Manzoor Ahmed[1], Edoardo Prediletto[1], Sarah E. Church[3], Briana M. Hudson[3], Sarah E. Warren[3], Paul M. McKeigue[4], Frances Humby[1], Michele Bombardieri[1], Michael R. Barnes[2], Myles J. Lewis[1,2,41] ✉, Costantino Pitzalis[1,41] ✉ and the R4RA collaborative group*

- Molecular and histologic profiling of joint tissue from randomized clinical trial of RA (R4RA).
- Demonstrated different treatment responses to 2 targeted biologic therapies.
- Lymphoid cells associated with response to rituximab.
- Myeloid cells associated with response to tocilizumab.
- Fibroid, pauci-immune phenotype represents a refractory endotype.

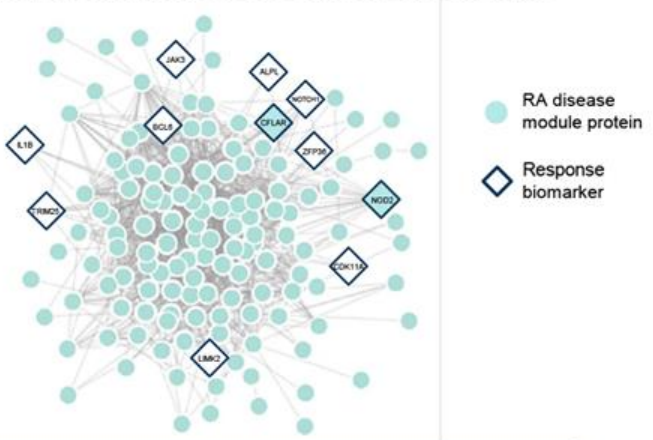
Blood test that predicts non-response to a TNF inhibitor

A Blood-Based Molecular Signature Response Classifier to Predict Inadequate Response to TNF Inhibitors[1]

Biomarkers in the MSRC

ALPL
ATRAID
BCL6
CDK11A
CFLAR
COMMD5
GOLGA1
IL1B
IMPDH2
JAK3
KLHDC3
LIMK2
NOD2
NOTCH1
SPINT2
SPON2
STOML2
TRIM25
ZFP36
BMI
Sex
Patient global assessment
Anti-CCP

Response Biomarkers Are in the Same Network Vicinity of the Human Interactome as the RA Disease Module



Patients with a molecular signature of nonresponse are unlikely to respond to TNFi treatment according to ACR, CDAI, and DAS28-CRP criteria of response at 3 and 6 months

1. Cohen S et al. *Rheumatol Ther*. 2021;8:1159-1176.

PeerView.com

QUESTIONS