Laboratory testing for rheumatoid arthritis

Antibodies to citrullinated peptides

...and some other points

The four major contributions of the immunology lab in the diagnosis of autoimmune diseasees

CCP → RA

Nucleosome → SLE

tTG → celiac disease

laminaribioside and chitobioside → IBD

The impact of RA on the European economy

- Direct costs (hospitalisations, treatments, diagnostics)

  €14 billion per year

- Indirect costs (productivity losses and informal care)

  €17 billion per year

- Within 10 years of the start of the condition,

  >50% of the patients are unable to work

Lundkvist J et al. *Eur J Health Econ* 2008, 8 (Suppl 2):S49

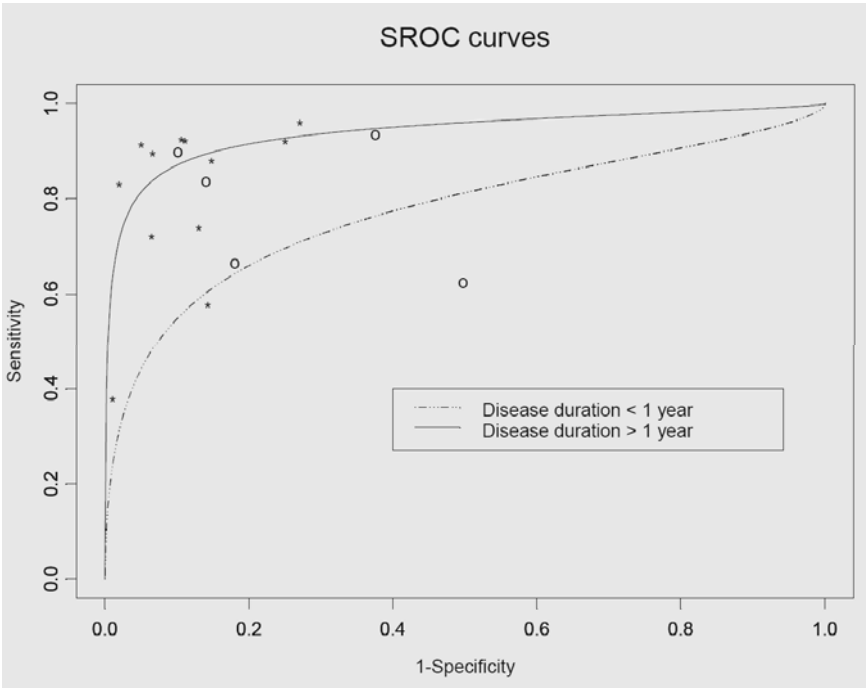
The ACR 1987 revised criteria for the diagnosis of RA

1. Morning stiffness
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

- 4 or more of these 7 criteria must be present
- First 4 criteria must have been present for at least 6 weeks

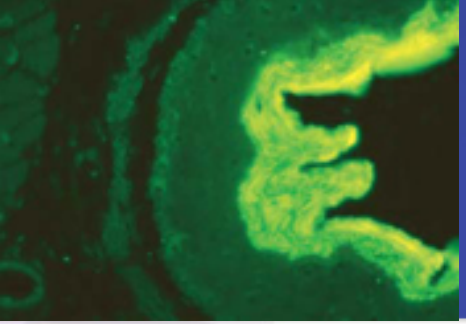
The ACR 1987 revised criteria for the diagnosis of RA

	Sn	Sp
early arthritis	80% (72-88%)	33% (24-43%)
established arthritis	80% (71-85%)	93% (86-97%)



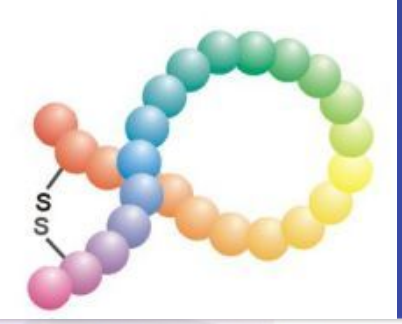
"… the specificity of the criteria
in early RA is low, and
they should not be used as diagnostic tools..."

Banal F et al. *Ann Rheum Dis* 2008 [Epub ahead of print]



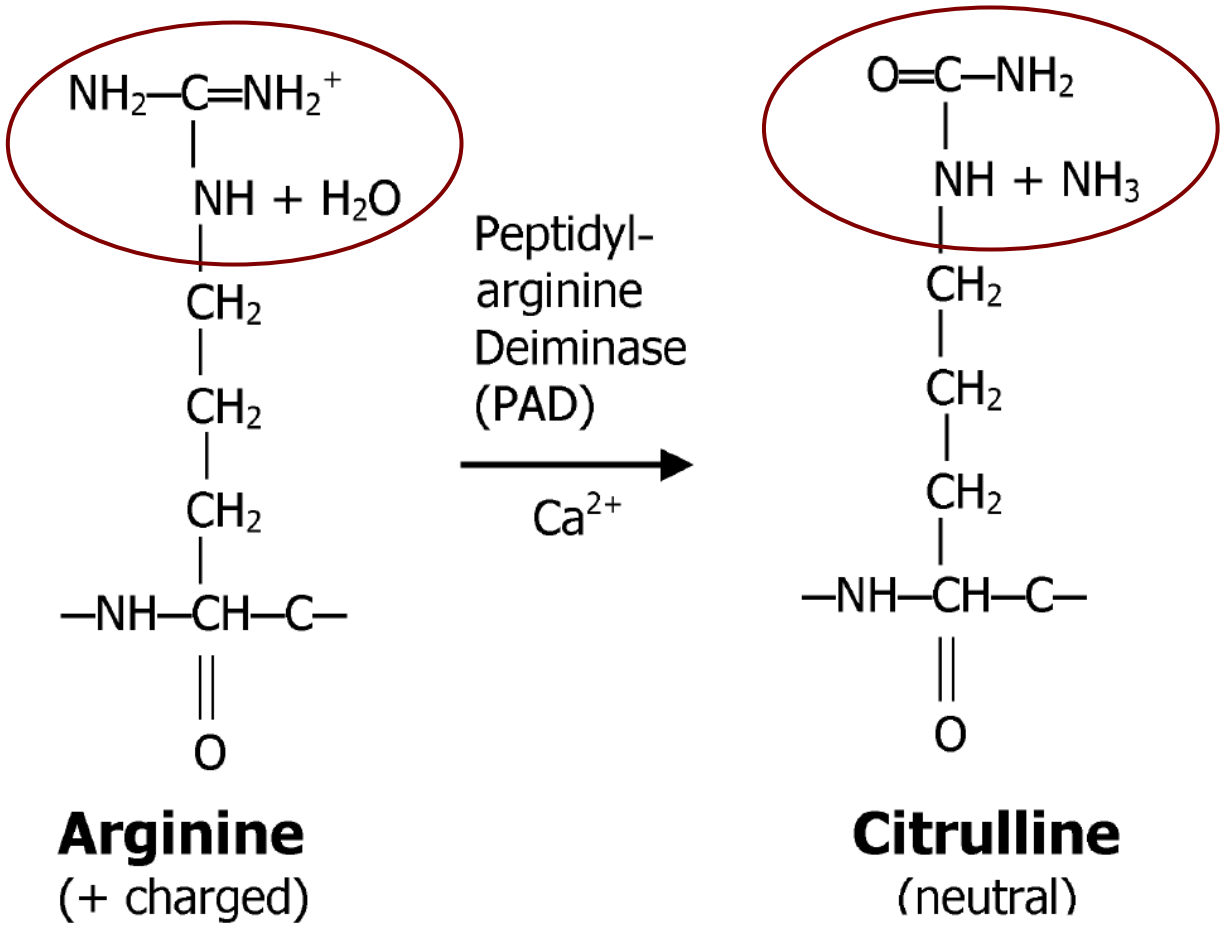
CCP history

1964	antiperinuclear antibodies
1979	anti-keratin antibodies
1995	anti-filaggrin antibodies
2000	CCP first generation (filaggrin derived)
2002	CCP second generation (library derived)
2005	CCP third generation



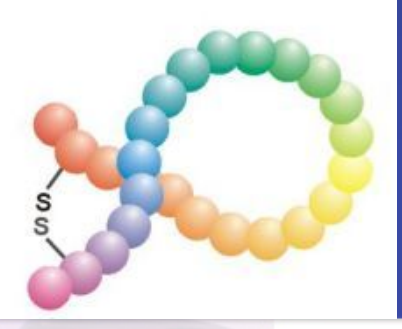
Citrullination

the posttranslational modification of protein-bound arginine into the non-standard amino acid citrulline



Arginine
(+ charged)

Citrulline
(neutral)



The role of CCP in the pathogenesis of RA

Inflammation
↓
Infiltration of PAD-containing inflammatory cells
↓
Death of PAD-containing cells
↓
Activation of PAD enzymes
↓
Protein citrullination

Genetic background (HLA-DRB1 "SE", *PADI* gene polymorphisms) and Environment (smoking, etc.)

Rheumatoid arthritis

Anti-CCP antibodies
↑
Immune response to citullinated proteins

the presence of SE does not seem to be associated in itself with RA, but specifically with the production of CCP

Diagnostic value

	RA patients			Healthy subjects n	Other RD n	**Sn** (%)	**Sp** (%)
	n	Age (yrs)	DD (yrs)				
CCP1	2234	55±7	1.5±1	326	1465	53±10	96±3
CCP2	6125	55±5	5±4.5	1561	4666	68±15	95±5
RF	8206	55.5±6	4±4	1865	5797	60±18	79±15

Anouac J et al. *Ann Rheum Dis* 2006;65:845

Specificity in different groups of diseases

Disease	No. of patients	Specificity, %
Systemic lupus erythematosus	1448	95.7
Sjögren's syndrome	915	96.7
Systemic sclerosis	342	96.5
Polymyositis	201	100
MCTD	94	97.9
UCTD	82	98.8
APS	11	100
Vasculitides	245	98.0
Cryoglobulinemia	73	97.3
Reactive arthritis	161	96.9
Crystal arthritis	73	97.3
Juvenile arthritis	519	94.6
Psoriatic arthritis	1003	93.5
Psoriasis	146	99.3
Ankylosing spondylitis	186	98.4
Spondiloarthritis	273	94.8
Osteoarthritis	387	97.1
Polymyalgia rheumatica	252	94.4
Fibromyalgia	10	100
Multiple sclerosis	47	100
Crohn's disease	62	96.8
Ulcerative colitis	62	100
Autoimmune thyroiditis	93	98.9
Autoimmune hepatitis	177	92.1
Primary biliary cirrhosis	49	95.9
Hepatitis C	588	98.8
Hepatitis C+cryoglobulinemia	105	100
Other viral infections	372	98.7
Lyme disease	90	96.0
Bacterial infections	318	92.5
Cancer	52	100
Miscellanea	119	98.3
Healthy subjects	4904	99.4
Total	13459	97.5

Bizzaro N. *Clin Chem Lab Med* 2007;45:150

PV in early undifferentiated arthritis

	EA (n)	**Follow-up** (mo)	**RA** (n) (diagnosis after follow-up)	**DD** at baseline (mo)	**OR** (95% CI)
CCP1	1327	15±5	603	<16	20 (14-31)
CCP2	2017	18±9	1026	<5	25 (18-35)

Anouac J et al. *Ann Rheum Dis* 2006;65:845

PV in healthy blood donors

(case-control studies, retrospective analysis)

	Sn (%)	**Sp** (%)	**OR** (95% CI)
CCP1	29 (<5 y before)	99.5	64.5 (8.5-489)
CCP2	4 (9 y before) 25 (>1.5 y before) 52 (<1.5 y before)	98	28 (8-95)

citrullination of antigens in the synovial membrane
begins many years before the appearance
of symptoms and development of the disease

Anouac J et al. *Ann Rheum Dis* 2006;65:845

Combination of CCP and SE

Diagnostic value

	Sn		Sp	
	%	95% CI	%	95% CI
CCP	37	25-51	98	93-100
SE	60	45-72	64	54-73
SESE	28	17-42	99	88-98
SE+CCP	28	17-42	95	94-100
SESE+CCP	14	6-27	99	94-100

Berglin E et al. *Arthritis Res Ther* 2004;6:R303

Combination of CCP and SE

Prognostic significance (2 yrs)

	OR	95% CI
CCP	25.1	2.8-222.2
SE	1.9	0.9-4.2
RF	2.6	1.2-5.2
SE+CCP	66.8	8.3-539.4
SE+RF	14.9	2.9-76.3

Berglin E et al. *Arthritis Res Ther* 2004;6:R303

Prognostic significance

CCP are correlated

with the development of *erosive lesions*,

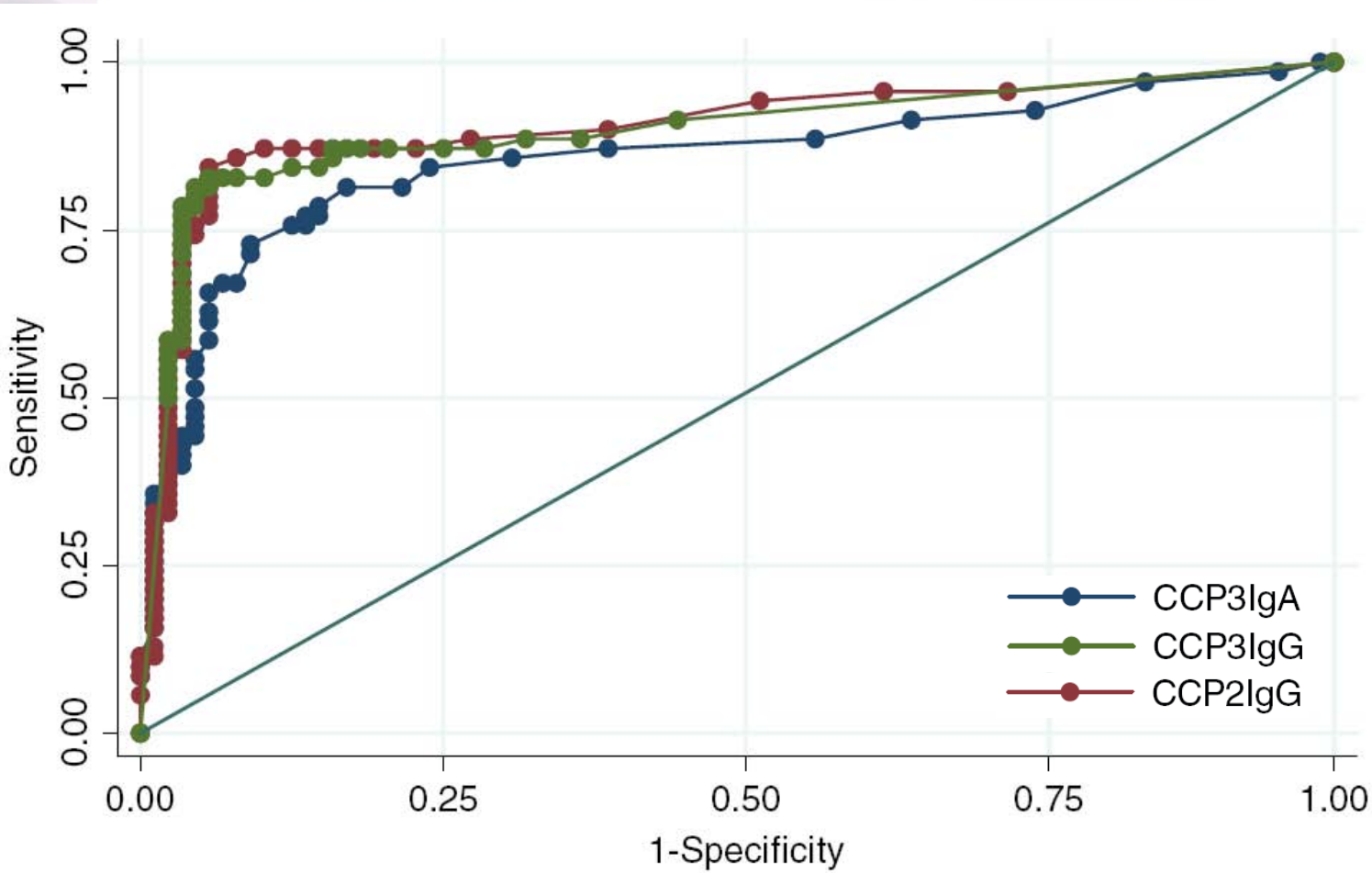
and

have considerable clinical potential

in selecting patients with early arthritis

who should receive aggressive treatment

Comparison of CCP2 and CCP3 ELISAs



Dos Anjos LME et al. *Clin Rheumatol* 2008 [Epub ahead of print]

Time to abandon RF?

- Measuring CCP antibodies in patients with RF>50 IU/L, adds little additional information
- The finding of RF in CCP(+) patients may predict extra-articular disease
- The finding of CCP in RF(–) patients predicts those who will develop progressive erosive disease
- RF(–)/CCP(–) patients with significant early inflammatory arthritis should be referred for specialist care. Their needs may be even greater than those with the worst prognosis who will respond to early aggressive therapy.

Symmons DPM. *Rheumatology* 2007;46:725