INTERNATIONAL JOURNAL OF
Clinical and Pharmaceutical Innovations
An International Peer Reviewed Open Access Journal

Review Article

ISSN (Online): 3142-8665
CODEN (USA): IJCPSM

2026, Volume 1, Issue 5, Page No: 131-145.

METABOLIC REPROGRAMMING IN RHEUMATOID ARTHRITIS: TARGETING FATTY-ACID METABOLISM AS A THERAPEUTIC STRATEGY

Kaustubh Bhardwaj[1]*, Shubham Biswas[2], Anie Jacob[1]

[1]Junior Resident, Department of Pharmacology & Therapeutics, King George's Medical University, UP, Lucknow-226003, India.
[2]Senior Resident, Department of Pharmacology & Therapeutics, King George's Medical University, UP, Lucknow-226003, India.

Article Info: **Received:** 19 June 2026, **Revised:** 09 July 2026, **Accepted:** 29 July 2026

***Corresponding Author: Kaustubh Bhardwaj**

Junior Resident, Department of Pharmacology & Therapeutics, King George's Medical University, UP, Lucknow-226003, India.

Citation:
Kaustubh Bhardwaj[1]*, Shubham Biswas[2], Anie Jacob[1]. (2026). Metabolic Reprogramming In Rheumatoid Arthritis: Targeting Fatty-Acid Metabolism As A Therapeutic Strategy. International Journal of Clinical and Pharmaceutical Innovations, 1(5), 131-145.
DOI: https://doi.org/10.5281/zenodo.21827315

ABSTRACT
Rheumatoid arthritis (RA), a chronic systemic autoimmune disorder, is estimated to affect roughly 1% of the population. Management has been transformed by conventional disease-modifying antirheumatic drugs (DMARDs), biologic agents and Janus kinase (JAK) inhibitors; however, sustained remission is still not attained by a considerable share of patients, and appreciable toxicity continues to be carried by the available options. Over the last decade, immunometabolism has been adopted as a framework through which the metabolic reprogramming of the effector cells driving synovitis, namely fibroblast-like synoviocytes (FLS), T lymphocytes, macrophages and osteoclast precursors, may be understood. What is of interest is that fatty-acid metabolism occupies a special position within that framework, since lipids are employed both as bioenergetic fuel and as precursors of pro-inflammatory and pro-resolving mediators. In the present narrative review, evidence is synthesized that lipid handling is disturbed in RA in a markedly cell-type-specific and frequently opposing fashion, and the agents acting upon uptake, de novo synthesis, desaturation, β-oxidation, thioesterase-mediated pool control, nuclear-receptor signaling, downstream lipid mediators, lipid peroxidation, sphingolipid signaling and microbiota-derived short-chain fatty acids are mapped. Candidate compounds are tabulated according to translational maturity. It is argued that translation is limited less by target discovery than by the context-dependent, tissue-divergent behaviour of these enzymes, by which the therapeutic window of systemically administered drugs is narrowed. Cell-selective delivery and disciplined repurposing are accordingly proposed as the most workable near-term strategies.

KEYWORDS: rheumatoid arthritis; immunometabolism; fatty-acid metabolism; metabolic reprogramming; fibroblast-like synoviocytes; drug repurposing.

1. INTRODUCTION

Persistent synovial inflammation, synovial hyperplasia and progressive destruction of cartilage and bone are the features by which rheumatoid arthritis is characterized, and disability, systemic comorbidity and shortened life expectancy continue to be associated with the disease.[1,3] Outcomes have been improved substantially by the present armamentarium, which comprises methotrexate and other conventional synthetic DMARDs, biologics directed against tumour necrosis factor and interleukin-6, and oral JAK inhibitors. However, treatment response is heterogeneous. A meaningful minority of patients are cycled through several agents without durable remission being achieved, and prescribing continues to be constrained by safety signals, among them the boxed cardiovascular and malignancy warnings attached to the JAK inhibitors.[3] Mechanistically distinct targets are therefore still being sought.

Immunometabolism, defined as the study of how metabolic state governs the fate and function of immune cells, has reframed the manner in which the rheumatoid joint is interpreted. A glycolytic, hypoxia-driven, reverse-Warburg shift within synovial tissue was emphasized by the earliest work.[6] Comparatively less attention has been directed towards fatty-acid metabolism; however, on pharmacological grounds this axis may be judged the more attractive of the two, for two reasons. First, lipids are dual-purpose molecules. The proliferation and membrane biogenesis upon which the invasive synovial phenotype depends are fuelled by them, while substrate is supplied at the same time to the eicosanoid and specialized pro-resolving mediator (SPM) systems by which inflammation is tuned.[11,23] Second, the enzymes of fatty-acid handling have already been drugged extensively in metabolic and oncologic disease, so that a ready supply of repurposable chemistry is made available.

Interest in this axis was crystallized recently by the description of obakulactone, a plant-derived triterpenoid by which experimental RA is alleviated through proteasomal degradation of acyl-CoA thioesterase 1 (ACOT1) and through restoration of unsaturated fatty-acid homeostasis.[1] Interestingly, that report is better read not as the arrival of a single candidate drug but as a proof of principle for a much broader target class. The target class itself, namely fatty-acid metabolism, rather than any individual molecule, is therefore taken here as the subject. The relevant pathways are outlined first; the cell-type-specific manner in which they are disturbed is then examined; the agents acting at each node are catalogued thereafter; and the translational obstacles by which the fate of this strategy in the clinic will be decided are appraised at the close.

2. Fatty-acid metabolism as a distinct axis of RA immunometabolism

Cellular handling of fatty acids may be conceptualized as a pipeline. Exogenous fatty acids are imported by transporters such as CD36 and by the fatty-acid-binding proteins.[4] De novo lipogenesis is carried out by acetyl-CoA carboxylase (ACC), through which acetyl-CoA is committed to malonyl-CoA, and by fatty-acid synthase (FASN), by which palmitate is assembled.[14] Saturated species are subsequently desaturated to monounsaturated ones by stearoyl-CoA desaturase-1 (SCD1).[16] Where energy is required, fatty acids are activated to acyl-CoAs and delivered into the mitochondrion by carnitine palmitoyltransferase-1 (CPT1) so that β-oxidation may proceed.[10] Acyl-CoAs are hydrolysed back to free fatty acids and coenzyme A by the acyl-CoA thioesterases (ACOTs), ACOT1 among them, and the size and composition of the intracellular free-fatty-acid pool are thereby governed.[11] Polyunsaturated fatty acids, and arachidonic acid in particular, are finally channelled into the cyclooxygenase and lipoxygenase routes by which prostaglandins and leukotrienes are produced, whereas resolvins and related pro-resolving mediators are generated from the omega-3 species.[23]

Every one of these steps constitutes a potential pharmacological node, and a different therapeutic logic is attached to each according to whether excess or deficiency is the pathological state. What is of interest is that the very same enzyme may warrant inhibition in one cellular setting yet preservation in another, a point that has been consistently under-appreciated. That theme is developed in the section which follows.

3. Cell-type-specific and bidirectional dysregulation of fatty-acid metabolism

The defining feature of fatty-acid reprogramming in RA is that uniformity across the cellular players of the joint is not observed. Rather, the direction in which dysregulation runs is found to diverge by cell type, and this divergence is regarded both as the central intellectual tension of the field and as the principal determinant of druggability. In Table 1 the reported alterations are summarized compartment by compartment, together with the direction of change and the evidence by which each is supported.

3.1 Fibroblast-like synoviocytes

FLS are the resident stromal cells by whose aggressive and invasive phenotype pannus formation and joint destruction are driven. In RA, mitochondrial β-oxidation of fatty acids is impaired within these cells. Interestingly, the same impairment is detected in fibroblasts obtained from individuals at risk of RA before synovial inflammation has become clinically apparent, from which it is argued that the metabolic shift may precede the disease and contribute to its initiation rather than merely follow it.[5] Lipid droplets are accumulated by RA-FLS, and both uptake and synthesis are rewired. CD36 is upregulated, and pathogenic activation is mediated by it through fatty-acid metabolic reprogramming together with mitochondrial dysfunction; when the transporter is blocked pharmacologically, synovial inflammation and bone erosion are reduced in

animal models.[4] De novo lipogenesis is implicated as well, in that the proliferative and invasive programme is supported by FASN activity.[7] A shift towards glycolysis alongside altered fatty-acid fluxes is likewise recapitulated when the metabolism of RA synovial fibroblasts is modelled computationally, which is consistent with a coordinated metabolic transformation rather than an isolated defect.[6]

3.2 T lymphocytes

A distinctive metabolic signature, centred upon mitochondrial dysfunction, is displayed by T cells in RA. β-oxidation of fatty acids is suppressed by underperforming mitochondria, and lipid droplets are accumulated in consequence; their contents are then repurposed for the construction of invasive membrane structures and for pro-inflammatory effector function.[8] Interestingly, those effector functions can be attenuated when fatty-acid metabolism is remodelled, as has been demonstrated in CD8+ T cells taken from patients with RA. It is indicated by this observation that the lipid programme should be regarded as a modifiable driver of pathogenic T-cell behaviour rather than as an inert correlate.[9] As was seen in FLS, the salient abnormality is a relative deficiency of oxidative fatty-acid handling.

3.3 Monocytes, macrophages and osteoclast precursors

In the monocyte to osteoclast lineage the picture is inverted. Here fatty-acid oxidation is found to be elevated rather than deficient. Carnitine palmitoyltransferase-1A (CPT1A) is upregulated in RA monocytes, fusion of osteoclast precursors is promoted by it, and a positive correlation with radiographic joint-damage scores has been reported.[10] Within this compartment, therefore, increased β-oxidation is pathogenic, and its inhibition would be considered therapeutically desirable, which is the opposite of what is implied by the FLS and T-cell data. Macrophage polarization between the pro-inflammatory (M1) and reparative (M2) states is linked to lipid-metabolic programming in comparable fashion, and experimental arthritis is ameliorated by agents through which the balance is shifted towards M2 dominance.[1]

3.4 The synovial lipidome and the lipid-mediator profile

The descriptive foundation upon which the enzymatic arguments set out above rest is supplied by direct measurement of joint lipids. When synovial fluid from patients with RA was screened by untargeted capillary LC-MS/MS, close to seventy discrete lipid components spanning several classes were identified, absolute quantification was achieved for lysophosphatidylcholine and phosphatidylcholine species, and pro-resolving mediators such as maresin 1, lipoxin A4 and resolvin D5 were shown to be detectable within the inflamed joint.[26] What is of interest is the conceptual weight carried by that last observation. It is established thereby that the resolution machinery is engaged in RA rather than absent, and the therapeutic question is accordingly reframed. No longer is it asked whether pro-resolving pathways are present in the joint; it is asked instead why inflammation is not terminated by them. Comparative analysis of paired infrapatellar fat pad and synovial fluid specimens has shown, in addition, that fatty-acid signatures are differentiated between RA and osteoarthritis within one and the same anatomical compartment, from which it is inferred that disease-specific rather than merely inflammation-generic information is carried by the lipid profile.[27] Total phospholipid concentration in synovial fluid is raised in inflammatory and degenerative arthropathy alike; however, the proportion of phospholipid relative to total lipid is lowered, and acyl-chain composition is shifted with inflammatory state. Such a pattern is consistent with a joint compartment in which free and neutral lipid species have been enriched at the expense of ordered membrane lipid.[28] For the present argument the practical value of these datasets is found less in diagnosis than in pharmacodynamics. A measurable and directionally predictable change in the synovial or plasma lipidome ought to be produced by any agent acting upon the nodes catalogued in Section 4. Such a readout is a considerably more tractable early-phase endpoint than DAS28, and go/no-go decisions could be de-risked by it before a large clinical trial is committed.

3.5 Fatty-acid-binding proteins: the intracellular shuttling layer

Between uptake at the membrane and metabolism at the enzyme there lies a transport layer which is frequently omitted from metabolic schematics. However, it is pharmacologically attractive for precisely that reason, being dispensable in most tissues. Lipids are chaperoned by the fatty-acid-binding proteins (FABPs) to metabolizing enzymes and to nuclear receptors, and the downstream programme activated by a given fatty acid is thereby determined. FABP4 is upregulated within synovial M1-polarized macrophages in RA, and synovitis, angiogenesis and cartilage degradation are promoted by it; disease was attenuated in murine arthritis when FABP4 was lowered in serum and in synovial macrophages by the selective inhibitor BMS309403 and by the dipeptidyl-peptidase-4 inhibitor anagliptin.[29] The human data are concordant and were in fact obtained earlier than the mechanistic work. In a study of forty patients with RA set against forty osteoarthritis controls, FABP4 was found to be significantly raised in serum ($p = 0.001$) and in synovial fluid ($p = 0.005$) once age, sex and body-mass index had been accounted for, and independent correlation with total and LDL cholesterol was demonstrated; however, no correlation with DAS28 was observed.[30] What is of interest is the dissociation itself. FABP4 is positioned by it as a candidate mechanistic link between synovial inflammation and the accelerated atherosclerosis of RA rather than as a marker of disease activity, and it is implied that a FABP4 inhibitor might be assessed on cardiovascular as well as on articular endpoints. A second and quite distinct

rationale is offered by the related isoform FABP5. In end-stage osteoarthritic synovium, release of the pronociceptive mediators IL-6, IL-8, CCL2 and CXCL1 was reduced when FABP5 was inhibited selectively, and in monoiodoacetate-induced arthritis the greater part of a pronociceptive transcriptional programme exceeding 6000 genes was suppressed by the inhibitor SBFI-103, with pain-related behaviour relieved accordingly.[31] Augmented endocannabinoid signaling has been held partly responsible for that effect. Retinoic acid is additionally shuttled by FABP5 to PPARβ/δ, whereas the same ligand is delivered by CRABP2 to the retinoic-acid receptors, with opposing consequences for proliferation and survival; FABP-directed agents may therefore act less by altering total lipid flux than by re-routing a ligand between competing nuclear receptors.[32] Whether an analgesic effect would be translated into a disease-modifying one in RA remains untested. Novelty in this domain is nonetheless represented by the prospect of symptomatic benefit obtained without immunosuppression.

3.6 The systemic dimension: dyslipidaemia and the lipid paradox

Dysregulation of fatty acids in RA is not confined to the joint, and the manner in which any lipid-directed therapy may be developed is constrained by the systemic phenotype. A two-fold to three-fold excess risk of cardiovascular disease is carried by patients with RA, and roughly half of the premature deaths recorded in this population are attributed to cardiovascular causes.[35] Counterintuitively, reduced total, LDL and HDL cholesterol are typically observed when disease is active. In a population-based incident cohort of 651 patients the association between cholesterol and cardiovascular events was found to be non-linear and inverted. A 3.3-fold increased risk was carried by a total cholesterol below 4 mmol/L (95% CI 1.5 to 7.2), whereas no excess risk was seen above that threshold; erythrocyte sedimentation rate, however, was shown to predict events independently (HR 1.2 per 10 mm/h increase, 95% CI 1.1 to 1.3).[33] This so-called lipid paradox is best construed as evidence that the informative variable is the inflammatory modification of lipoproteins rather than their concentration. Cholesterol catabolism is accelerated by an excess of pro-inflammatory cytokines, HDL sub-particle composition is remodelled and its antioxidant and reverse-transport capacity degraded, and oxidation together with other post-translational modification of LDL is promoted.[34] Consistent with that reading, measured cholesterol is raised by effective DMARD therapy at the same time as cardiovascular risk is lowered.[35] Three practical consequences are entailed for the programme sketched in this review. First, benefit and harm in RA are poorly surrogated by conventional lipid panels, so lipoprotein function or particle-level measures ought to be incorporated into trials of fatty-acid-directed agents rather than concentrations alone. Second, a population already at elevated cardiovascular risk is being entered by agents with recognized on-target dyslipidaemic liabilities, of which the hypertriglyceridaemia produced by ACC inhibition is the clearest instance, and the evidentiary bar is raised accordingly. Third, and more constructively, the single largest cause of mortality in RA would be addressed by an agent through which both synovial inflammation and lipoprotein quality were improved; such a dual endpoint constitutes a stronger clinical and commercial proposition than joint counts considered alone.

Taken together, mitochondrial β-oxidation is seen to be simultaneously deficient in fibroblasts and T cells yet excessive in osteoclast precursors. However, no single global intervention directed at fatty-acid oxidation could be expected to benefit all three compartments, since one may be helped while another is harmed by a systemically delivered inhibitor. Novelty in this domain is therefore constrained less by the discovery of targets than by this bidirectionality, which is the crux of the pharmacological challenge addressed below.

Table 1: Reported fatty-acid-metabolic alterations in rheumatoid arthritis by compartment, with direction of change and supporting evidence.

Compartment	Principal alteration	Direction	Evidence base	Ref.
Fibroblast-like synoviocytes	Mitochondrial β-oxidation impaired; lipid-droplet accumulation; CD36 and FASN upregulated	Oxidation ↓; uptake and synthesis ↑	Synovium from established and at-risk individuals; collagen-induced arthritis	4,5,7
T lymphocytes	Mitochondrial dysfunction suppresses β-oxidation; droplet lipid diverted to invasive membrane structures	Oxidation ↓	Primary human RA T cells, including CD8+	8,9
Monocytes and osteoclast precursors	CPT1A upregulated; promotes precursor fusion; correlates	Oxidation ↑	Human RA monocytes; erosion scoring	10

Compartment	Principal alteration	Direction	Evidence base	Ref.
	with radiographic damage			
Synovial macrophages	FABP4 secreted by M1-polarized cells drives synovitis, angiogenesis and cartilage degradation	Lipid shuttling ↑	Human synovium and serum (n=40 vs 40 OA); murine arthritis	29,30
Synovial fluid lipidome	~70 lipid species detectable; maresin 1, lipoxin A4 and resolvin D5 present; phospholipid share of total lipid falls	Composition shifted	Untargeted and targeted LC-MS/MS of human RA synovial fluid	26,28
Synovial tissue redox state	Iron deposition and lipid-peroxidation products; GPX4/SLC7A11 profile suggests ferroptosis resistance	Peroxidation ↑; susceptibility ↓	Human synovium; patient-derived RA-FLS	36,37,38
Systemic circulation	Total, LDL and HDL cholesterol reduced in active disease; HDL antioxidant function impaired	Concentration ↓; atherogenicity ↑	Population-based incident cohort (n=651); mechanistic reviews	33,34
Gut lumen	Acetate, propionate and butyrate reduced with depletion of SCFA-producing commensals	SCFA ↓	Human RA cohorts; murine arthritis models	39,40,41
Sphingolipid axis	SphK1, S1P and $S1P_1$ elevated in synovium; $S1P_1$/$S1P_3$ drive FLS survival and migration; $S1P_2$/$S1P_3$ raise IL-6 and IL-8; S1P induces RANKL	Signaling ↑	Human rheumatoid synovium and FLS; collagen-induced arthritis	43,44,45,46
Pro-resolving mediator tone	Resolvins, protectins, maresins and lipoxins present but functionally insufficient; plasma SPM profile tracks DMARD response	Resolution capacity ↓	Human early-RA plasma; SKG and adjuvant-induced arthritis	49,52

4. Pharmacological targeting of fatty-acid metabolic nodes

Those agents which act upon the fatty-acid metabolism relevant to RA are summarized in Table 2, where they are ordered along the metabolic pipeline. For most of the nodes a striking divergence is observed between the furthest clinical development attained by a compound in any indication whatever and the depth of the evidence obtained in RA itself. What is of interest is that the chemistry has frequently been matured while the RA proof of concept has not.

Table 2: Pharmacological agents acting on fatty-acid metabolic nodes implicated in rheumatoid arthritis, ordered along the lipid-handling pipeline. "Most-advanced stage" denotes the compound's furthest clinical development in any indication; "RA-specific evidence" is restricted to disease-specific data.

Metabolic node	Representative compound(s)	Mechanism	Most-advanced stage (any indication)	RA-specific evidence	Key liability
Uptake: CD36	Sulfo-N-succinimidyl oleate (SSO)	Irreversible CD36 fatty-acid transporter inhibitor; starves RA-FLS of imported lipid	Preclinical tool compound only	↓ synovial inflammation and bone erosion in collagen-induced arthritis (CIA) rats	Not drug-like; no clinical programme; CD36 broadly expressed → selectivity concern
Synthesis: FASN	Denifanstat (TVB-2640); orlistat, C75, cerulenin (older tools)	Fatty-acid synthase inhibition; blocks de novo palmitate synthesis	Denifanstat: Phase 2b positive (FASCINATE-2, MASH), FDA Breakthrough Therapy (2025), Phase 3-ready; Phase 3 completed in China (acne). Older tools preclinical / orlistat approved (obesity)	None direct; ↓ Th17 generation and ↓ IL-1β ex vivo; RA named as target indication in FASN-inhibitor patents	On-target dermatologic effects (alopecia, dry eye); older tools have off-target activity; RA efficacy unproven
Synthesis: ACC	Firsocostat (GS-0976); clesacostat (PF-05221304)	Liver-targeted acetyl-CoA carboxylase inhibition; upstream of FASN	Phase 2 (MASH); clesacostat monotherapy discontinued, advanced only in combination (with DGAT2 inhibitor ervogastat)	None	On-target hypertriglyceridaemia (drove combination-only development); RA untested
Desaturation: SCD1	Aramchol; A939572, MF-438 (tools)	Partial stearoyl-CoA desaturase-1 modulation; ↓ monounsaturated-FA synthesis	Aramchol Phase 3 (ARMOR, MASH); tools preclinical	Implicated via the ACOT1 → SCD1 axis; no direct RA data	Systemic SCD1 blockade causes skin/eye/sebaceous toxicity in animals
β-oxidation: CPT1A	Etomoxir; perhexiline, ranolazine (repurposing)	Carnitine palmitoyltransferase-1 inhibition; blocks mitochondrial FA import	Etomoxir halted (Phase 2 heart failure); perhexiline/ranolazine approved (cardiology)	Target validated: CPT1A-driven FAO promotes osteoclast fusion, correlates with radiographic damage (inhibition is the desired direction)	Etomoxir hepatotoxicity; perhexiline neuro-/hepatotoxicity requiring drug monitoring
Thioesterase: ACOT1	Obakulactone (OL)	Natural triterpenoid; drives ubiquitin-proteasome degradation of ACOT1 → ↓ free-FA supply and SCD1 →	Preclinical (rat + cell)	↓ joint swelling, cytokines and FLS proliferation in CFA rats; direct ACOT1 binding (Kd ≈ 6 μM)	Modest affinity, high doses; ACOT1 protective in heart and fasting liver → narrow therapeutic window

Metabolic node	Representative compound(s)	Mechanism	Most-advanced stage (any indication)	RA-specific evidence	Key liability
		suppresses JAK-STAT/PI3K-AKT			
Signaling: PPARγ	Pioglitazone	PPARγ agonist; anti-inflammatory + insulin-sensitizing	Approved (type 2 diabetes)	RA crossover RCT: ~9% DAS28-CRP reduction, ↓ CRP and insulin resistance	Peripheral oedema, weight gain, fracture and heart-failure cautions
Signaling: HMG-CoA reductase	Atorvastatin, rosuvastatin	Mevalonate-pathway inhibition; pleiotropic anti-inflammatory (lipid-adjacent)	Approved (dyslipidaemia); several RA trials	TARA RCT (atorvastatin 40 mg adjunct, n=116): ~50% CRP reduction, DAS28/swollen-joint improvement; 15-RCT meta-analysis supportive	Myopathy; disease-modifying effect modest, primary value is cardiovascular-risk reduction
Signaling: AMPK	Metformin	AMPK activator; rebalances glycolysis/FAO	Approved (type 2 diabetes)	Preclinical rationale + preliminary human signals; a definitive RA RCT was not confirmed, hypothesis-generating	GI tolerance; effect size unestablished; evidence base thin
Lipid mediators: COX / 5-LOX	NSAIDs; zileuton	Block prostaglandin (COX) / leukotriene (5-LOX) synthesis from arachidonate	Approved	NSAIDs standard symptomatic therapy; not disease-modifying	GI/renal/cardiovascular (NSAIDs); hepatic (zileuton)
Lipid mediators: substrate-level	Marine n-3 PUFA (EPA/DHA); γ-linolenic acid	Shift eicosanoid profile; substrate for pro-resolving mediators (resolvins)	Approved supplement; extensive RA RCT programme	Strongest human evidence: 16/20 RA trials positive; meta-analysis of 18 RCTs / 1018 patients	Modest effect size; GI upset; dose and product-quality variability

Abbreviations: ACC, acetyl-CoA carboxylase; ACOT1, acyl-CoA thioesterase 1; CFA, complete Freund's adjuvant; CIA, collagen-induced arthritis; CPT1, carnitine palmitoyltransferase 1; DAS28, Disease Activity Score in 28 joints; DGAT2, diacylglycerol acyltransferase 2; EPA/DHA, eicosapentaenoic/docosahexaenoic acid; FA(O), fatty acid (oxidation); FASN, fatty-acid synthase; FLS, fibroblast-like synoviocyte; MASH, metabolic-dysfunction-associated steatohepatitis; NSAID, non-steroidal anti-inflammatory drug; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RA, rheumatoid arthritis; RCT, randomised controlled trial; SCD1, stearoyl-CoA desaturase 1.

4.1 Fatty-acid uptake: CD36

The import channel by which the fibroblast lipid programme is fed has been addressed pharmacologically by one agent only, the irreversible inhibitor sulfo-N-succinimidyl oleate (SSO), which remains a preclinical tool. When CD36 is blocked by SSO, synovial inflammation and bone erosion are reduced in collagen-induced arthritis, and the target is validated thereby. However, no drug-like CD36 inhibitor has yet been taken into clinical development, and selectivity concerns are raised by the broad tissue distribution of the transporter.[4]

4.2 De novo synthesis: FASN and ACC

This is the most drug-rich node of all, since substantial chemistry has been generated by oncology and steatohepatitis programmes. The early FASN tools, among them cerulenin, C75, platensimycin and the repurposed lipase inhibitor orlistat, were mechanistically informative; however, their utility was limited by off-target activity.[14] The clinically important molecule is denifanstat (TVB-2640), an oral FASN inhibitor by which the primary endpoints of a phase 2b trial in metabolic-dysfunction-associated steatohepatitis (MASH) were met, for which FDA Breakthrough Therapy designation was granted, and by which a phase 3 programme in acne has been completed.[15] Its relevance to RA is supported on mechanistic grounds. Generation of T helper 17 (Th17) cells and release of interleukin-1β are both reduced ex vivo when FASN is inhibited, and RA is named explicitly among the target indications within FASN-inhibitor patent estates.[14] One step upstream, hepatic lipogenesis is lowered by the ACC inhibitors firsocostat and clesacostat; however, on-target hypertriglyceridaemia is provoked by them. Clesacostat monotherapy was discontinued for that reason and is now being advanced only in combination with a diacylglycerol acyltransferase-2 inhibitor.[17,18] No ACC inhibitor has been tested in RA to date.

4.3 Desaturation: SCD1

SCD1 is the node at which obakulactone acts indirectly, since downstream SCD1 is lowered when ACOT1 is degraded by that compound.[1] Direct SCD1 pharmacology does exist. Phase 3 for MASH has been reached by aramchol, a partial SCD1 modulator for which anti-fibrotic effects have been reported, and tool inhibitors such as A939572 and MF-438 are employed experimentally. However, no dedicated RA programme has been established, and cutaneous and ocular toxicity is produced in animals when SCD1 is blocked systemically.[16]

4.4 β-oxidation: CPT1A

Because oxidation driven by CPT1A is pathogenic within the osteoclast lineage, a CPT1 inhibitor would be regarded as therapeutically rational for bone erosion.[10] The classic tool compound, etomoxir, is instructive as a cautionary tale. Phase 2 for congestive heart failure was reached by it; however, hepatotoxicity was caused, and isozyme selectivity is lacking.[19] Liabilities of their own are carried by the partial FAO inhibitors used in cardiology and available for repurposing, namely perhexiline and ranolazine, among which the requirement for therapeutic drug monitoring with perhexiline should be noted. It is at this node that the directionality hazard is most concretely illustrated, since the oxidative deficiency of fibroblasts and T cells could be aggravated by the very inhibition that is desired for osteoclast precursors.

4.5 Thioesterase-mediated pool control: ACOT1

Obakulactone constitutes the single worked example at this node and is therefore treated here as a case study. In rats with arthritis induced by complete Freund's adjuvant, joint swelling was reduced by the compound, cartilage and synovial architecture were normalized, macrophages were shifted from M1 to M2 dominance, Th17 differentiation was restrained, and serum IL-1β, IL-6, IL-17 and TNF-α were lowered in dose-dependent fashion.[1] Direct binding to ACOT1 with a dissociation constant of approximately 6 μM was confirmed by biophysical assay; ubiquitin-proteasome degradation of ACOT1 was enhanced by the compound, SCD1 was reduced in consequence, and JAK-STAT together with PI3K-AKT signaling was suppressed within synovial fibroblasts.[1] It is best regarded as a preclinical proof of concept for a novel node rather than as a clinical candidate. The affinity is modest, the effective doses are high and, most importantly, ACOT1 is protective within cardiac and fasting-hepatic tissue, where oxidative stress is restrained and PPARα signaling supported by its activity.[11,12,13] A plausible therapeutic-window risk is therefore carried by systemic degradation of ACOT1.

4.6 Nuclear-receptor and upstream signaling

The transcriptional and energy-sensing machinery by which fatty-acid metabolism is governed is modulated by several approved agents for which direct RA data are available. When the PPARγ agonist pioglitazone was added to standard therapy in a crossover RCT, a reduction of roughly 9% in DAS28-CRP was obtained and both C-reactive protein and insulin resistance were improved, although peripheral oedema was incurred.[20] Statins, by which the mevalonate pathway is inhibited and pleiotropic anti-inflammatory effects are exerted, produced a reduction in CRP of about one half together with improvement in swollen-joint counts in the TARA trial of adjunctive atorvastatin, and corroboration was subsequently supplied by meta-analysis; however, their principal value in RA is still held to lie in the reduction of cardiovascular risk.[21,22] The AMPK activator metformin is proposed frequently as a repurposing candidate. However, robust randomized evidence in RA was not identified, and the agent should at present be treated as hypothesis-generating only.

4.7 Downstream lipid mediators

It is at the lipid-mediator layer that fatty-acid metabolism is connected to both the oldest and the best-validated pharmacology in RA. Cyclooxygenase within the arachidonic-acid cascade is acted upon by the non-steroidal anti-inflammatory drugs, while the leukotriene arm is targeted by 5-lipoxygenase inhibitors such as zileuton; symptomatic rather than disease-modifying benefit is furnished by both classes. The standout intervention is supplementation with marine omega-3 polyunsaturated fatty acids, by which eicosanoid synthesis is shifted towards less inflammatory species and substrate is supplied for the pro-resolving mediators. Clinical benefit was reported by the majority of roughly

twenty RA trials, and effects upon fatty-acid distribution, inflammation and disease activity were confirmed by a meta-analysis of eighteen randomized trials in more than a thousand patients.[23,24,25] Omega-3 supplementation is thus regarded as the existence proof of the field, since it is demonstrated thereby that RA outcomes in humans are altered when fatty-acid metabolism is manipulated.

The strongest single piece of that evidence deserves to be stated at trial level, because it is routinely under-weighted. In a double-blind randomized trial conducted in DMARD-naive patients whose RA had been present for less than twelve months, high-dose fish oil supplying 5.5 g/day of EPA plus DHA was compared against a low-dose control of 0.4 g/day, all upon a background of treat-to-target triple therapy with methotrexate, sulfasalazine and hydroxychloroquine; dose escalation was governed throughout by a pre-specified algorithm.[42] Failure of triple therapy, defined as the addition of leflunomide, was taken as the primary endpoint. Such failure was recorded markedly less often in the fish-oil arm (HR 0.28, 95% CI 0.12 to 0.63; p = 0.002, and 0.24 once smoking, shared epitope and baseline anti-CCP had been adjusted for), and the rate at which first ACR remission was attained was approximately doubled (HR 2.17, 95% CI 1.07 to 4.42; p = 0.03). No difference between the groups was detected in methotrexate dose, DAS28, functional score or adverse events.[42] Two features render this result unusually instructive for the present argument. First, benefit was expressed as a drug-sparing and remission-rate effect while the conventional continuous measures of disease activity were left unchanged. Interestingly, such a pattern would have been missed altogether by a trial powered upon DAS28 alone, and a caution is thereby issued for the design of future trials of metabolic agents. Second, plasma n-3 concentrations were correlated with the odds of remission, so that a target-engagement biomarker of exactly the kind lacking at the other nodes of this section was provided. Marine omega-3 supplementation accordingly functions within this review both as an existence proof and as a methodological template.

4.8 Lipid peroxidation and ferroptosis as a consequence of polyunsaturated-fatty-acid handling

A node which is absent from the classical pipeline, yet mechanistically situated downstream of it, is the oxidative fate of those polyunsaturated fatty acids that are esterified by ACSL4 and LPCAT3 into membrane phosphatidylethanolamines. Where the resulting lipid hydroperoxides cannot be reduced by glutathione peroxidase 4 (GPX4), iron-dependent lipid peroxidation is propagated to lethality, and ferroptosis is the outcome. The rheumatoid synovium is a plausible setting for such chemistry. Iron is deposited in osteoarthritic and rheumatoid synovium alike, although in substantially greater quantity in the latter, and products of lipid peroxidation are demonstrable within RA synovial tissue.[36] What is of interest is that pharmacological proof of concept has been obtained in both directions at this single node. Selective induction of ferroptosis within the hyperplastic fibroblast compartment is attractive, since resistance to apoptosis is characteristic of RA-FLS. Accumulation of lipid peroxide and ferroptotic death are triggered in RA synoviocytes by the GPX4 inhibitor RSL3, and when liver kinase B1 (LKB1) was knocked down in RA-FLS obtained from patient synovium, lipid peroxidation and cell death were increased ($p < 0.01$), by which the LKB1 to AMPK axis is implicated as an endogenous brake capable of being released therapeutically.[37,38] Conversely, anti-inflammatory benefit in murine arthritis has been shown for ferroptosis inhibitors such as liproxstatin-1, and the reported expression data are not uniform. In one series ACSL4 was found to be reduced in RA synovium and FLS, whereas ferritin heavy chain 1, GPX4 and SLC7A11 were comparatively increased, a profile by which active resistance to ferroptosis rather than susceptibility is suggested.[37] The apparent contradiction need not be treated as a conflict of evidence. The directionality problem identified in Section 3 is simply restated at a different node, because cell-selective delivery, and not a systemically administered pro-ferroptotic or anti-ferroptotic agent, would be required if fibroblasts were to be sensitized to lipid peroxidation while chondrocytes and cardiomyocytes were protected from it. Until such selectivity is available, ferroptosis in RA is better regarded as a target-validation tool, and as a candidate mechanism of action for agents already in use, than as a stand-alone therapeutic strategy.

4.9 Microbiota-derived short-chain fatty acids

An exogenous, microbial arm is also possessed by fatty-acid metabolism in RA. The short-chain fatty acids (SCFAs), chiefly acetate, propionate and butyrate, are products of bacterial fermentation by which free-fatty-acid receptors are engaged and histone deacetylases inhibited, and they are found to be reduced in patients with RA and in murine models of arthritis in parallel with a loss of SCFA-producing commensals.[39] Mechanistically, $Foxp3^{+}$ regulatory T cells and IL-10-producing regulatory B cells are expanded by SCFAs while activation of pro-inflammatory effector T cells is restrained. Arthritis is suppressed in murine models by butyrate; experimental arthritis is suppressed by microbiota-derived metabolites through amplification of aryl-hydrocarbon-receptor activation within regulatory B cells; and B-cell differentiation is directed by SCFAs through the FFA2 receptor.[40,41] Among the clinical and translational correlates reported are reduced faecal butyrate and propionate in RA, restoration of the Th17 to Treg balance with suppression of NLRP3-inflammasome activation, and improvement in disease-activity scores following high-fibre dietary intervention.[39] Inclusion of this arm is merited on three grounds. It is the only node in this review that can be addressed by diet and by living biotherapeutics rather than by small molecules; it is situated upstream of the intracellular enzymes discussed above, since immune-cell differentiation rather than

synovial lipid flux is acted upon; and a favourable safety profile is carried by its interventions, which suits them to adjunctive and preventive use. However, the evidence base is materially weaker than is implied by the numerical precision of individual reports. Much of it is derived from small, heterogeneous and largely single-centre studies in which SCFA measurement methods have varied, and adequately powered randomized trials with joint-specific endpoints remain outstanding.

4.10 Sphingolipid signaling: sphingosine kinases and S1P receptors

Glycerolipids and free fatty acids have been the concern of the pipeline discussed so far. However, a parallel lipid class, namely the sphingolipids, supplies what is arguably the most clinically advanced repurposing opportunity in this entire review, and its omission from most immunometabolic accounts of RA is difficult to justify. Sphingosine-1-phosphate (S1P) is generated by two sphingosine kinases, SphK1 and SphK2, and signals are transduced by it through five G-protein-coupled receptors. Sphingosine kinase 1, S1P and $S1P_1$ are all found to be elevated within rheumatoid synovium. There, synoviocyte proliferation and cytokine-induced cyclo-oxygenase-2 expression are promoted by $S1P_1$ signaling, and prostaglandin E_2 production is generated in consequence.[43,44] $S1P_1$, $S1P_2$ and $S1P_3$ are expressed by human RA-FLS, and the labour is divided among the receptor subtypes. Survival is dependent upon $S1P_1$; migration is driven by $S1P_1$/$S1P_3$; and secretion of IL-6 and IL-8 is enhanced by $S1P_2$/$S1P_3$. All of these effects are amplified by TNF-α, so that the cytokine-rich synovial environment and the sphingolipid axis are mutually reinforcing rather than independent.[44] The bone compartment is implicated as well. RANKL expression in synovial fibroblasts and $CD4^+$ T cells is upregulated by S1P through a Gi/Go-dependent mechanism, and the axis is thereby linked directly to osteoclastogenesis and to erosion.[45] Causality at the receptor level has been demonstrated in vivo, since the development of collagen-induced arthritis was associated with upregulation of $S1P_3$ upon fibroblast-like synoviocytes acting through increased IL-6 production.[46]

What distinguishes this node from the others catalogued above is that the chemistry is not merely clinical-stage but approved outright. Fingolimod (FTY720), a sphingosine analogue and functional S1P-receptor antagonist, is licensed for relapsing multiple sclerosis, and later-generation modulators of greater receptor selectivity, namely ozanimod, siponimod and etrasimod, have been approved in multiple sclerosis and in inflammatory bowel disease. Relevantly, SphK2 is strongly expressed within rheumatoid synovial fibroblasts, and apoptosis is induced in those cells by FTY720, by which a joint-directed mechanism additional to lymphocyte sequestration is indicated.[47] Set against this, well-characterized liabilities are carried by the class, among them first-dose bradycardia, macular oedema, elevation of hepatic enzymes, lymphopenia and infection risk. Such liabilities are tolerated in multiple sclerosis; however, careful justification would be demanded in a disease for which effective therapy already exists. Within the tiering scheme of Section 5 this node is uniquely placed, since approved chemistry, human safety data at scale and a mechanistic RA rationale drawn from human synovial tissue are all present, and yet no adequately powered RA trial has been conducted. Novelty in this domain is therefore available at unusually low risk, and on the evidence assembled here this node is judged the single most obvious candidate for a proof-of-concept repurposing study across the whole fatty-acid and lipid-signaling space.

4.11 Specialized pro-resolving mediators: agonizing resolution rather than blocking inflammation

Omega-3 supplementation was treated in Section 4.7 as the provision of substrate. The mediators themselves, however, constitute a pharmacological strategy that is quite distinct, and one by which the logic of every other agent in this review is inverted; instead of an inflammatory enzyme being inhibited, an agonist is supplied for the endogenous programme through which inflammation is terminated. The specialized pro-resolving mediators (SPMs), comprising the D-series and E-series resolvins, the protectins and maresins derived from DHA and EPA, and the lipoxins derived from arachidonic acid, act upon defined receptors that include GPR32, ALX/FPR2 and LGR6. Neutrophil apoptosis, macrophage efferocytosis and M2 polarization are stimulated by them, and immunosuppression is not incurred.[48] In human peripheral-blood lymphocytes, cytokine production by activated $CD8^+$, Th1 and Th17 cells was reduced by resolvin D1, resolvin D2 and maresin 1, de novo induction of regulatory T cells was promoted through GPR32, and proliferative capacity was left intact.[48] The arthritis-specific data are consistent and both effector arms of RA pathology are covered by them. When paw tissue from SKG arthritic mice was subjected to lipid-mediator metabololipidomics, SPMs including resolvin D5 were found to be elevated and correlated with disease activity; Th17 differentiation was subsequently suppressed by resolvin D5, differentiation of regulatory T cells was facilitated, proliferation of $CD4^+$ T cells was inhibited and osteoclast differentiation was attenuated.[49] Pannus formation was suppressed by resolvin D1 through upregulation of miR-146a-5p and consequent lowering of connective-tissue growth factor[50], while anti-hyperalgesic effects were produced in adjuvant-induced arthritis in rats by the resolvin D-series precursor together with aspirin-triggered resolvin D1.[51] It is indicated by the latter finding that pain, as well as structural disease, may be addressed by this class.

The most consequential clinical observation, however, is diagnostic rather than therapeutic in character. In deeply phenotyped patients with early RA, DMARD responsiveness at six months was predicted by baseline plasma concentrations of resolvin D4, 10S,17S-

dihydroxy-docosapentaenoic acid, 15R-lipoxin A4 and maresin 1 derived from n-3 docosapentaenoic acid; the separation between responders and non-responders was maintained at six months, and SPM concentrations were seen to fall in those patients in whom therapy was resisted.[52] This is the closest approach the field has yet made to a validated lipid biomarker of prospective clinical utility, and the biomarker-stratification priority of Section 7 is converted by it from an aspiration into a testable protocol. Two caveats temper that enthusiasm. First, SPMs are chemically unstable, are inactivated rapidly and are difficult to formulate, which is why no SPM has been advanced far as a drug despite two decades of biology; stable analogues and agonists of the biosynthetic pathway are therefore the more plausible route. Second, it was noted in Section 3.4 that SPMs are already present within inflamed human synovium.[26] It is implied thereby that failure of resolution in RA reflects defective downstream signaling or premature catabolism of the mediators rather than simple deficiency, in which case the supply of further mediator may not suffice and agonism at the receptor level is the better-posed intervention.

5. Translational maturity of candidate agents

Viewed through a development lens, the candidates may be sorted into four tiers. In the first are placed those interventions already supported by randomized evidence in RA and safe to be combined with standard care, of which the marine omega-3 fatty acids are the sole example. In the second are gathered repurposing candidates for which a human RA signal exists alongside well-characterized safety, namely pioglitazone, the statins and, more tentatively, metformin. The third comprises molecules that have reached clinical stage in other diseases and are mechanistically plausible in RA, yet for which no RA proof of concept whatever has been obtained; the FASN, ACC and SCD1 inhibitors drawn from the MASH and oncology pipelines belong here. In the fourth are found preclinical tool compounds by which a target is validated without a viable clinical molecule being supplied, namely SSO for CD36, etomoxir for CPT1 and obakulactone for ACOT1. It is made explicit by this tiering that the near-term opportunities of the field are located less in novel discovery than in the disciplined repositioning of chemistry that already exists.

The quality of the evidence supporting each tier, and not merely its quantity, ought to be stated explicitly, since equal security is not enjoyed by the four. Randomized controlled data with clinical endpoints in RA are possessed by the first tier alone.[42] Small single-centre randomized or crossover studies with surrogate outcomes are drawn upon by the second, and in the case of metformin nothing beyond observational and mechanistic inference is available. No RA-specific efficacy data of any kind are held by the third tier; its plausibility is transitive, being inferred from enzyme expression in RA tissue together with clinical activity in an unrelated indication, and a poor historical record has been compiled by transitive plausibility in rheumatology. Animal and in vitro data constitute the fourth tier, frequently from a single model and often obtained with tool compounds whose off-target activity has been either documented or left unassessed. Before any tier-three or tier-four agent were committed to an RA trial, a minimum viable dataset ought to be demanded. Target expression and pathway activity should be demonstrated in human RA synovial tissue rather than in cell lines; efficacy should be shown in at least two mechanistically distinct arthritis models; ex vivo activity should be established upon primary human RA-FLS or upon immune cells derived from patients; and a measurable pharmacodynamic biomarker of target engagement should be available in blood or synovial fluid. That standard is currently approached only by the omega-3 programme and, in part, by those directed at CD36 and ACOT1. However, more is served by stating the gap plainly than by presenting all nodes as though they were equivalently promising.

Two of the nodes introduced above are accommodated awkwardly within this four-tier scheme and are better described as a fifth category, in which approved chemistry in an unrelated indication is combined with human RA tissue evidence but with no RA trial. The clearest instance is furnished by the sphingosine-1-phosphate receptor modulators, since regulatory approval and large safety databases are carried by fingolimod, ozanimod, siponimod and etrasimod, and demonstrable activity of the target within rheumatoid synovium has been established.[43,47] The mirror-image position is occupied by the specialized pro-resolving mediators, for which exceptional biological and biomarker credentials in human RA have been documented[52]; however, no viable drug-like molecule is available, because chemical instability is inherent to the mediators themselves. What is of interest is that the two failure modes of the field are defined between them, namely a good drug for which no RA trial has been run and a good target for which no drug exists. That distinction is of practical consequence, since only the former can be resolved by a decision to conduct a study.

6. Challenges: context-dependence, therapeutic window and delivery

The liability recurring across every node is context-dependence, and it should be recognized as a pharmacological problem rather than a merely biological one. Mitochondrial β-oxidation is protective within fibroblasts and T cells yet pathogenic within osteoclast precursors, so that help and harm could be delivered simultaneously by a systemic FAO inhibitor and the therapeutic window eroded in the process.[5,8,10] The same tension is illustrated by ACOT1 across organs, since pathogenicity is exhibited in synovium while protection is afforded in heart and liver.[1,11,13] The strategic implication is that the frontier is situated in cell-selective delivery and in the engineering of therapeutic

index, whether by joint-targeted or cell-directed formulation, by prodrug strategy, or by exploitation of cell-specific dependencies, rather than in the identification of further targets, of which no shortage is apparent.

A second and more optimistic theme concerns timing. Because lipid-metabolic abnormalities are detected within FLS before clinical synovitis has appeared in at-risk individuals, fatty-acid metabolism may be positioned as a driver lying upstream of overt inflammation, and the prospect of a preventive window in seropositive at-risk populations is raised accordingly.[5] Metabolic intervention is thereby reframed as potentially disease-intercepting rather than purely symptomatic.

A third theme, acknowledged less often than the other two, is methodological. The evidence assembled in this review is heterogeneous in a manner by which its poolability is limited. Extraction chemistry, analytical platform and normalization strategy all differ between synovial lipidomic studies, so that absolute lipid concentrations are seldom rendered comparable across reports.[26,28] Cohort sizes are small, frequently fewer than twenty patients per arm. Specimens are commonly obtained at joint replacement, by which end-stage disease is selected for and the metabolic state of the early synovium, the very tissue that any preventive strategy would target, is probably misrepresented. The problem is compounded by the animal models. Collagen-induced and adjuvant-induced arthritis are dominated by innate and Th17 mechanisms, bone erosion is modelled imperfectly by them, and inbred rodents are differentiated from humans in desaturation and elongation capacity, which is precisely the biology under study. Cell-culture work is conducted typically in serum-containing media of undefined lipid composition, so that an uncontrolled variable is introduced into experiments whose readout is lipid metabolism itself. Finally, most of the negative space remains invisible, since agents by which arthritis models were not modified are under-reported; the apparent uniformity of positive findings across nodes should therefore be discounted accordingly. None of this undermines the central thesis. However, it does argue that quantitative effect sizes in this literature be treated as indicative rather than adopted as parameters for trial design.

7. Future directions

Several priorities are entailed by the foregoing. (i) Repurposing-first clinical evaluation. The strategy would be tested at manageable risk if adequately powered RA trials were conducted upon agents already in human use, for instance the FASN or SCD1 inhibitors emerging from MASH programmes, or if the evaluation of pioglitazone and the statins as adjuncts were intensified. (ii) Combination design. Metabolic agents are most plausibly deployed alongside DMARDs, by which the combination logic already adopted in the ACC and DGAT2 field for the management of on-target toxicity would be mirrored. (iii) Biomarker-guided stratification. Patients whose disease is metabolically driven, and in whom response is therefore most likely, could be identified by synovial and circulating lipidomic signatures. (iv) Delivery innovation. Cell-selective exposure should be pursued through nanocarrier and joint-targeted approaches so that the therapeutic window may be widened. (v) Target-selectivity work. For nodes such as ACOT1 it must be established whether joint-restricted modulation can be achieved without cardioprotective and hepatoprotective functions being compromised. (vi) Ferroptosis selectivity. It must be determined whether the hyperplastic, apoptosis-resistant fibroblast can be rendered selectively vulnerable to lipid peroxidation without chondrocytes or myocardium being sensitized, which is the pivotal question at that node.[37] (vii) Dietary and microbial trials. Adequately powered randomized evaluation of high-fibre or SCFA-directed intervention with joint-specific endpoints is achievable at modest cost, and the only arm of this axis accessible without a new chemical entity would be tested thereby.[39] (viii) Standardized lipidomic endpoints. Consensus should be reached upon a small panel of synovial and plasma lipid species measured on harmonized platforms, so that mechanistically distinct agents may be compared upon a common pharmacodynamic scale. (ix) Cardiovascular co-primary endpoints. Given that cardiovascular risk in RA is driven by lipoprotein modification rather than by lipid concentration, trials of fatty-acid-directed agents are unusually well placed for articular and vascular benefit to be measured together.[33,34]

Trial design for the preventive window deserves separate comment, since it is at once the most distinctive opportunity offered by this axis and the most demanding methodologically. Where intervention is contemplated in anti-CCP-positive at-risk individuals before clinical synovitis has declared itself, a safety profile must be possessed by which exposure of people who may never develop disease can be tolerated. Omega-3 supplementation, dietary and microbial approaches, and repurposed agents backed by decades of safety data are therefore favoured immediately over novel enzyme inhibitors. Enrichment strategies are required in addition, since progression occurs in only a minority of at-risk individuals. Interestingly, metabolic markers may be made to serve a double duty here. If impaired fibroblast β-oxidation is detectable pre-clinically[5], then a lipid-metabolic signature could be employed simultaneously as the criterion by which the cohort is enriched and as the mechanistic rationale for the intervention under test.

8. CONCLUSION

Fatty-acid metabolism has been matured from a descriptive feature of the rheumatoid joint into a credible class of therapeutic target. It is indicated by the evidence that lipid handling is reprogrammed in RA in a cell-type-specific and frequently opposing manner, that numerous druggable nodes are distributed along the fatty-acid

pipeline, and that a rich supply of clinical-stage chemistry is made available by adjacent metabolic and oncologic indications. That the axis is therapeutically actionable in humans has already been demonstrated by omega-3 supplementation. The decisive obstacle is not the discovery of targets but the tissue-divergent, context-dependent roles played by the enzymes concerned, by which cell-selective delivery and careful engineering of the therapeutic index are demanded. The most realistic route from the present preclinical abundance to clinical benefit is offered by a development strategy that is repurposing-led, combination-oriented and biomarker-guided. Two immediate opportunities are made prominent by the evidence assembled here. A proof-of-concept trial of an approved sphingosine-1-phosphate receptor modulator should be undertaken in RA, and the plasma pro-resolving-mediator signature should be validated prospectively as a predictor of DMARD response. Both are achievable with molecules and assays that already exist, and the discovery of a new target is required by neither.

Declarations

Author contributions: K B did conceptualisation and writing of first draft. S B and A J gave valuable inputs during revision of manuscript.

Funding: The authors received no specific funding for this work.

Conflicts of interest: None.

Data availability: Not applicable; this is a narrative review of published literature.

REFERENCES

1. Liu H, Yang L, Yang Y, et al. Obakulactone alleviates rheumatoid arthritis by promotion of ACOT1 degradation via the ubiquitin-proteasome pathway and restoration of unsaturated fatty acid homeostasis. Engineering, 2026; 56: 341-360.
2. An updated and comprehensive review of Phellodendri amurensis Cortex: ethnobotany, geographical distribution, phytochemistry, quality control, and pharmacology. Molecules, 2026; 31(8): 1318.
3. Kiełbowski K, Plewa P, Bratborska AW, Bakinowska E, Pawlik A. JAK inhibitors in rheumatoid arthritis: immunomodulatory properties and clinical efficacy. Int J Mol Sci., 2024; 25(15): 8327. doi:10.3390/ijms25158327
4. Hao J, Zheng J, Liu C, Lu J, Tan M, Li J, Mao J, Yu Y, Wang H, Zhang Y, Shen H. CD36-mediated fatty acid metabolic reprogramming activates synovial fibroblasts and promotes rheumatoid arthritis progression. Int Immunopharmacol, 2025; 167: 115594. doi:10.1016/j.intimp.2025.115594
5. de Jong TA, Semmelink JF, Denis SW, van de Sande MGH, Houtkooper RHL, van Baarsen LGM. Altered lipid metabolism in synovial fibroblasts of individuals at risk of developing rheumatoid arthritis. J Autoimmun, 2023; 134: 102974. doi:10.1016/j.jaut.2022.102974
6. Aghakhani S, Soliman S, Niarakis A. Metabolic reprogramming in rheumatoid arthritis synovial fibroblasts: a hybrid modeling approach. PLoS Comput Biol., 2022; 18(12): e1010408.
7. Su Y, Li Y, et al. Inhibition of aberrant activated fibroblast-like synoviocytes in rheumatoid arthritis by a Leishmania peptide via regulation of fatty acid synthesis metabolism. Adv Sci., 2025; 12: 2409154.
8. Weyand CM, Wu B, Goronzy JJ. The metabolic signature of T cells in rheumatoid arthritis. Curr Opin Rheumatol, 2020; 32(2): 159-167. doi:10.1097/BOR.0000000000000683
9. Kraus FV, Keck S, Klika KD, et al. Reduction of proinflammatory effector functions through remodeling of fatty acid metabolism in CD8+ T cells from rheumatoid arthritis patients. Arthritis Rheumatol, 2023; 75: 1098-1109.
10. CPT1A-mediated fatty acid oxidation promotes precursor osteoclast fusion in rheumatoid arthritis. Front Immunol, 2022; 13: 838664.
11. Franklin MP, Sathyanarayan A, Mashek DG. Acyl-CoA thioesterase 1 (ACOT1) regulates PPARα to couple fatty acid flux with oxidative capacity during fasting. Diabetes, 2017; 66(8): 2112-2123.
12. Pasini E, Baciu C, Angeli M, Arendt B, Pellegrina D, Reimand J, Patel K, Tomlinson G, Mazhab-Jafari MT, Kotra LP, Fischer S, Allard JP, Humar A, Bhat M. Acyl-CoA thioesterase 1 contributes to transition of steatosis to metabolic-associated steatohepatitis. Int J Hepatol, 2024; 2024: 5560676. doi:10.1155/2024/5560676
13. Liu Y, Zeng L, Yang Y, Chen C, Wang D, Wang H. Acyl-CoA thioesterase 1 prevents cardiomyocytes from doxorubicin-induced ferroptosis via shaping the lipid composition. Cell Death Dis., 2020; 11(9): 756. doi:10.1038/s41419-020-02948-2
14. O'Farrell M, Duke G, Crowley R, Buckley D, Martins EB, Bhattacharya D, Friedman SL, Kemble G. FASN inhibition targets multiple drivers of NASH by reducing steatosis, inflammation and fibrosis in preclinical models. Sci Rep., 2022; 12(1): 15661. doi:10.1038/s41598-022-19459-z
15. Loomba R, Bedossa P, Grimmer K, et al. Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: a multicentre, double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol, 2024; 9(12): 1090-1100. doi:10.1016/S2468-1253(24)00246-2
16. Ratziu V, Yilmaz Y, Lazas D, et al. Aramchol improves hepatic fibrosis in metabolic dysfunction-associated steatohepatitis: results of multimodality assessment. Hepatology, 2025; 81(3): 932-946.
17. Alkhouri N, Lawitz E, Noureddin M, DeFronzo R, Shulman GI. GS-0976 (firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH). Expert Opin

Investig Drugs, 2020; 29(2): 135-141. doi:10.1080/13543784.2020.1668374
18. Efficacy and safety of ervogastat alone and in combination with clesacostat in patients with biopsy-confirmed MASH and F2-F3 fibrosis (MIRNA): a phase 2 randomised study. Lancet Gastroenterol Hepatol, 2025.
19. McGuffee RM, McCommis KS, Ford DA. Etomoxir: an old dog with new tricks. J Lipid Res., 2024; 65(9): 100604. doi:10.1016/j.jlr.2024.100604
20. Ormseth MJ, Oeser AM, Cunningham A, et al. Peroxisome proliferator-activated receptor γ agonist effect on rheumatoid arthritis: a randomised controlled trial. Arthritis Res Ther., 2013; 15(5): R110.
21. McCarey DW, McInnes IB, Madhok R, et al. Trial of atorvastatin in rheumatoid arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet, 2004; 363(9426): 2015-2021.
22. Li GM, Zhao J, Li B, et al. The anti-inflammatory effects of statins on patients with rheumatoid arthritis: a systematic review and meta-analysis of 15 randomised controlled trials. Autoimmun Rev., 2018; 17(3): 215-225.
23. Akbar U, Yang M, Kurian D, Mohan C. Omega-3 fatty acids in rheumatic diseases: a critical review. J Clin Rheumatol, 2017; 23(6): 330-339. doi:10.1097/RHU.0000000000000563
24. Wang W, Xu Y, Zhou J, Zang Y. Effects of omega-3 supplementation on lipid metabolism, inflammation, and disease activity in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Clin Rheumatol, 2024; 43(8): 2479-2488. doi:10.1007/s10067-024-07040-0
25. Veselinovic M, Vasiljevic D, Vucic V, et al. Clinical benefits of n-3 PUFA and γ-linolenic acid in patients with rheumatoid arthritis. Nutrients, 2017; 9(4): 325.
26. Giera M, Ioan-Facsinay A, Toes R, et al. Lipid and lipid mediator profiling of human synovial fluid in rheumatoid arthritis patients by means of LC-MS/MS. Biochim Biophys Acta., 2012; 1821(11): 1415-1424.
27. Mustonen AM, Käkelä R, Lehenkari P, Huhtakangas J, Turunen S, Joukainen A, Kääriäinen T, Paakkonen T, Kröger H, Nieminen P. Distinct fatty acid signatures in infrapatellar fat pad and synovial fluid of patients with osteoarthritis versus rheumatoid arthritis. Arthritis Res Ther., 2019; 21(1): 124. doi:10.1186/s13075-019-1914-y
28. Ben-Trad L, Matei CI, Sava MM, Filali S, Duclos ME, Berthier Y, Guichardant M, Bernoud-Hubac N, Maniti O, Landoulsi A, Blanchin MG, Miossec P, Granjon T, Trunfio-Sfarghiu AM. Synovial extracellular vesicles: structure and role in synovial fluid tribological performances. Int J Mol Sci., 2022; 23(19): 11998. doi:10.3390/ijms231911998
29. Guo D, Lin C, Lu Y, Guan H, Qi W, Zhang H, Shao Y, Zeng C, Zhang R, Zhang H, Bai X, Cai D. FABP4 secreted by M1-polarized macrophages promotes synovitis and angiogenesis to exacerbate rheumatoid arthritis. Bone Res., 2022; 10(1): 45. doi:10.1038/s41413-022-00211-2
30. Andrés Cerezo L, Kuklová M, Hulejová H, Vernerová Z, Pešáková V, Pecha O, Veigl D, Haluzík M, Pavelka K, Vencovský J, Šenolt L. The level of fatty acid-binding protein 4, a novel adipokine, is increased in rheumatoid arthritis and correlates with serum cholesterol levels. Cytokine, 2013; 64(1): 441-447. doi:10.1016/j.cyto.2013.05.001
31. Gordon C, Trainor J, Shah RJ, Studholme K, Gelman A, Doswell F, Sadar F, Giovannetti A, Gershenson J, Khan A, Nicholson J, Huang Z, Spurgat M, Tang SJ, Wang H, Ojima I, Carlson D, Komatsu DE, Kaczocha M. Fatty acid binding protein 5 inhibition attenuates pronociceptive cytokine/chemokine expression and suppresses osteoarthritis pain: a comparative human and rat study. Osteoarthritis Cartilage, 2024; 32(3): 266-280. doi:10.1016/j.joca.2023.11.010
32. Mosquera N, Rodriguez-Trillo A, Mera-Varela A, Gonzalez A, Conde C. Uncovering cellular retinoic acid-binding protein 2 as a potential target for rheumatoid arthritis synovial hyperplasia. Sci Rep., 2018; 8(1): 8731. doi:10.1038/s41598-018-26027-x
33. Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis., 2011; 70(3): 482-487.
34. Yan J, Yang S, Han L, Ba X, Shen P, Lin W, Li T, Zhang R, Huang Y, Huang Y, Qin K, Wang Y, Tu S, Chen Z. Dyslipidemia in rheumatoid arthritis: the possible mechanisms. Front Immunol, 2023; 14: 1254753. doi:10.3389/fimmu.2023.1254753
35. Oiegar R, Pop D. Cardiovascular risk assessment in patients with rheumatoid arthritis. J Clin Med., 2025; 14(18): 6461. doi:10.3390/jcm14186461
36. Zhao T, Yang Q, Xi Y, Xie Z, Shen J, Li Z, Li Z, Qin D. Ferroptosis in rheumatoid arthritis: a potential therapeutic strategy. Front Immunol, 2022; 13: 779585. doi:10.3389/fimmu.2022.779585
37. Wang Z, Bai X, Zhang H, Yang M, Liu M, Nie T, Li T, Zhang M, Wang X, Wang J, Han J, Liu X. Targeting the ferroptosis pathway for rheumatoid arthritis: molecular mechanisms and prospects for inhibitor development. Front Immunol, 2025; 16: 1610121. doi:10.3389/fimmu.2025.1610121
38. Lee HR, Yoo SJ, Kim J, Kang SW. The LKB1-AMPK signaling axis modulates ferroptosis in fibroblast-like synoviocytes derived from rheumatoid arthritis. Biomedicines, 2025; 13(2): 321.
39. Pang A, Pu S, Pan Y, Huang N, Li D. Short-chain fatty acids from gut microbiota restore Th17/Treg balance in rheumatoid arthritis: mechanisms and therapeutic potential. J Transl Autoimmun, 2025; 11: 100316. doi:10.1016/j.jtauto.2025.100316
40. Rosser EC, Piper CJM, Matei DE, et al. Microbiota-derived metabolites suppress arthritis by amplifying

aryl-hydrocarbon receptor activation in regulatory B cells. Cell Metab, 2020; 31(4): 837-851.e10.
41. Yao Y, Cai X, Zheng Y, et al. Short-chain fatty acids regulate B cell differentiation via the FFA2 receptor to alleviate rheumatoid arthritis. Br J Pharmacol, 2022; 179(17): 4315-4329.
42. Proudman SM, James MJ, Spargo LD, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. Ann Rheum Dis., 2015; 74(1): 89-95.
43. Kitano M, Hla T, Sekiguchi M, et al. Sphingosine 1-phosphate/sphingosine 1-phosphate receptor 1 signaling in rheumatoid synovium: regulation of synovial proliferation and inflammatory gene expression. Arthritis Rheum, 2006; 54(3): 742-753.
44. Lai WQ, Melendez AJ, Leung BP. Role of sphingosine kinase and sphingosine-1-phosphate in inflammatory arthritis. World J Biol Chem., 2010; 1(11): 321-326. doi:10.4331/wjbc.v1.i11.321
45. Takeshita H, Kitano M, Iwasaki T, Kitano S, Tsunemi S, Sato C, Sekiguchi M, Azuma N, Miyazawa K, Hla T, Sano H. Sphingosine 1-phosphate (S1P)/S1P receptor 1 signaling regulates receptor activator of NF-κB ligand (RANKL) expression in rheumatoid arthritis. Biochem Biophys Res Commun., 2012; 419(2): 154-159. doi:10.1016/j.bbrc.2012.01.103
46. Inoue T, Kohno M, Nagahara H, Murakami K, Sagawa T, Kasahara A, Kaneshita S, Kida T, Fujioka K, Wada M, Nakada H, Hla T, Kawahito Y. Upregulation of sphingosine-1-phosphate receptor 3 on fibroblast-like synoviocytes is associated with the development of collagen-induced arthritis via increased interleukin-6 production. PLoS One, 2019; 14(6): e0218090. doi:10.1371/journal.pone.0218090
47. Kamada K, Arita N, Tsubaki T, et al. Expression of sphingosine kinase 2 in synovial fibroblasts of rheumatoid arthritis contributing to apoptosis by a sphingosine analogue, FTY720. Pathol Int., 2009; 59(6): 382-389.
48. Chiurchiù V, Leuti A, Dalli J, Jacobsson A, Battistini L, Maccarrone M, Serhan CN. Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses. Sci Transl Med., 2016; 8(353): 353ra111. doi:10.1126/scitranslmed.aaf7483
49. Yamada H, Saegusa J, Sendo S, Ueda Y, Okano T, Shinohara M, Morinobu A. Effect of resolvin D5 on T cell differentiation and osteoclastogenesis analyzed by lipid mediator profiling in the experimental arthritis. Sci Rep., 2021; 11(1): 17312. doi:10.1038/s41598-021-96530-1
50. Sun W, Ma J, Zhao H, Xiao C, Zhong H, Ling H, Xie Z, Tian Q, Chen H, Zhang T. Resolvin D1 suppresses pannus formation via decreasing connective tissue growth factor caused by upregulation of miRNA-146a-5p in rheumatoid arthritis. Arthritis Res Ther., 2020; 22(1): 61. doi:10.1186/s13075-020-2133-2
51. Lima-Garcia JF, Dutra RC, da Silva K, et al. The precursor of resolvin D series and aspirin-triggered resolvin D1 display anti-hyperalgesic properties in adjuvant-induced arthritis in rats. Br J Pharmacol, 2011; 164(2): 278-293.
52. Gomez EA, Colas RA, Souza PR, Hands R, Lewis MJ, Bessant C, Pitzalis C, Dalli J. Blood pro-resolving mediators are linked with synovial pathology and are predictive of DMARD responsiveness in rheumatoid arthritis. Nat Commun, 2020; 11(1): 5420. doi:10.1038/s41467-020-19176-z