PAI-1 as a Universal Systemic Integrator Node: A Unified Relative Permissiveness Network Synthesis Across Cancer, Neurodegeneration, Acute Infection, Fibrosis, and Immune Biology

Michael Warrington

Independent Researcher

AI assistance provided by Claude (Anthropic, claude-sonnet-4-6)h

Correspondence: available via Zenodo

RPN Series Note

This paper is the unified synthesis of a seven-paper series. Individual papers address: prostate cancer; breast, ovarian, and endometrial cancer; Alzheimer's disease and repurposed drugs; COVID-19 and Long COVID; idiopathic pulmonary fibrosis; and bacterial vaccination and immune checkpoint biology. All are available in the Zenodo RPN repository. This synthesis supersedes the earlier unified paper (Series Paper 3) by incorporating the full scope of the series.

Abstract

The Relative Permissiveness Network (RPN) framework proposes that chronic disease arises when successive biological perturbations shift a regulatory molecular network from a resilient, multi-pathway-balanced healthy state into a stable attractor state dominated by one or a small number of high-centrality integrator nodes. Once dominant, these integrators lock the network against therapeutic reversal through self-reinforcing feedback — making single-target interventions systematically insufficient regardless of the biological plausibility of the individual mechanism.

Across a seven-paper series, we identify plasminogen activator inhibitor-1 (PAI-1, SERPINE1) as a universal systemic integrator node whose dominant expression drives attractor lock-in across multiple distinct pathological domains: cancer progression and chemoresistance (prostate, breast, ovarian, endometrial); neurodegeneration through the PAI-1/BDNF maturation axis and astrocyte senescence (Alzheimer's disease); biphasic innate immune failure and cytokine storm (COVID-19 and Long COVID); fibrotic lung remodelling through the PAI-1/proteasome/p53 molecular brake and persistent wound state (idiopathic pulmonary fibrosis); and immune evasion through the PAI-1/PD-L1/JAK-STAT3 checkpoint axis relevant to bacterial vaccination and cancer immunotherapy.

The rs1799889 insertion-deletion polymorphism at the PAI-1 promoter (4G/5G) is the central conditioning variable across all disease domains. The 4G/4G genotype produces constitutively higher PAI-1 expression — approximately 25% higher at baseline, amplifiable to six-fold higher under IL-1β stimulation — creating the pre-conditions for PAI-1 integrator dominance in susceptible tissue contexts. Across six disease domains, 4G/4G genotype is predicted to condition the efficacy of PAI-1-modulating interventions, most importantly aspirin, statins, senolytics, bacterial vaccination, and checkpoint inhibitor therapy. All predictions are falsifiable and testable retrospectively in the UK Biobank using existing genotyping, medication records, and multi-disease registry linkage.

The unified clinical message is precise: PAI-1 is not a generic inflammatory marker but a pharmacogenomically stratifiable systemic integrator whose therapeutic relevance is concentrated in the 4G/4G subpopulation across cancer, neurodegeneration, infection, and fibrosis simultaneously. Genotyping at rs1799889 — a single assay — identifies the subpopulation for whom aspirin, statins, and PAI-1 inhibitors represent precision medicine rather than population-level interventions.

Keywords: PAI-1, SERPINE1, rs1799889, 4G/5G polymorphism, Relative Permissiveness Network, attractor state, integrator node, aspirin, statins, senolytics, cancer, prostate cancer, breast cancer, ovarian cancer, endometrial cancer, Alzheimer's disease, COVID-19, Long COVID, idiopathic pulmonary fibrosis, LL-37, BDNF, PD-L1, bacterial vaccination, trained immunity, Coley's toxins, pharmacogenomics, UK Biobank, repurposed drugs, precision medicine

---

1. The Central Argument

The dominant paradigm in drug development for chronic disease is target identification followed by single-agent therapeutic development against that target. This paradigm has succeeded in oncology for diseases driven by single strong oncogenes — BCR-ABL in CML, BRAF V600E in melanoma — and in infectious disease where single pathogen proteins can be neutralised. It has failed systematically in complex chronic diseases including late-stage cancer, Alzheimer's disease, idiopathic pulmonary fibrosis, and the post-acute sequelae of viral infection, where even mechanistically excellent single-target therapies produce partial, transient, or population-heterogeneous effects.

The RPN framework proposes a systems-level explanation for this failure: complex chronic diseases are attractor states maintained by multi-node regulatory architectures, not single-pathway linear cascades. In such states, a high-centrality stabilisation hub —

a molecular node whose activity simultaneously constrains multiple downstream effector systems — maintains the attractor against single-target perturbation through redundant stabilisation. Effective therapeutic disruption requires identifying the stabilisation hub and targeting it either directly or through combination strategies that simultaneously perturb multiple load-bearing nodes.

This paper argues, across seven domains of disease, that PAI-1 is the most broadly documented and pharmacogenomically accessible stabilisation hub in human chronic disease. Its cross-disease relevance is not coincidental — it reflects PAI-1's position at the intersection of fibrinolysis, inflammation, cellular senescence, vascular biology, neuroplasticity, immune checkpoint regulation, and extracellular matrix homeostasis. A node at the intersection of this many regulatory systems will achieve integrator dominance across multiple tissue contexts under the right conditions of genetic pre-conditioning and environmental loading.

The rs1799889 polymorphism makes this pharmacogenomically actionable: genotype determines whether PAI-1 is or is not the load-bearing integrator in a given patient's disease attractor. Stratifying by genotype transforms PAI-1-modulating repurposed drugs from population-level interventions with inconsistent trial results into precision medicines with concentrated, predictable efficacy in a genetically identified subpopulation.

---

2. The Framework: Attractor States, Integrator Nodes, and the 4G/5G Pre-Conditioner

2.1 Attractor States in Chronic Disease

Biological regulatory networks exhibit attractor dynamics: stable configurations that the system preferentially occupies and to which it returns after perturbation. Healthy tissue function corresponds to a broad, shallow attractor basin — many perturbations are absorbed and the system returns to the healthy baseline. Chronic disease corresponds to a narrow, deep attractor basin — the system is stabilised in a pathological configuration and resists perturbation back toward the healthy state.

The depth of a disease attractor — the magnitude of perturbation required to exit it — increases with disease progression, as stabilising feedback loops are established and self-reinforcing cellular substrates (senescent cell populations, fibrotic matrix architectures, persistent vascular endotheliopathy) accumulate. This is why early intervention consistently outperforms late intervention across disease domains, and why therapeutic windows close as disease progresses.

2.2 PAI-1 as a Universal Stabilisation Hub

An integrator node functions as a stabilisation hub when its activity simultaneously constrains multiple downstream systems that are individually necessary for the disease attractor. PAI-1's hub status derives from its concurrent regulation of:

Plasmin generation — controlling ECM degradation, growth factor activation, complement modulation, BDNF maturation, Abeta clearance, and LL-37 activation

Cellular senescence — through the PAI-1/proteasome/p53 non-proteolytic mechanism that stabilises p53 independently of DNA damage, locking ATII cells (IPF), astrocytes (AD), and tumour microenvironment cells (cancer) in permanent growth arrest

TGF-beta sustenance — through suppression of plasmin-mediated TGF-beta inactivation, maintaining the pro-fibrotic and pro-tumorigenic TGF-beta signal in fibrosis and cancer

Immune checkpoint regulation — through the PAI-1/LRP1/uPAR/JAK-STAT3 pathway that drives PD-L1 expression, enabling tumour immune evasion

Vascular homeostasis — through fibrinolytic balance, platelet regulation, and endothelial function relevant to cardiovascular disease, stroke, and COVID-19 endotheliopathy

Neuroplasticity — through the pro-BDNF/mBDNF maturation axis, where PAI-1-mediated plasmin suppression blocks pro-BDNF cleavage to the synaptic-survival-supporting mBDNF form

No other single molecule has documented regulatory influence across all six of these systems. This is why PAI-1 integrator dominance produces such similar attractor phenomenology across superficially distinct diseases: the common hub generates common attractor properties despite different tissue contexts and different initiating pathologies.

2.3 The 4G/5G Polymorphism as Attractor Pre-Conditioner

The rs1799889 insertion-deletion polymorphism operates at the PAI-1 promoter. The 4G allele binds only a transcriptional activator; the 5G allele binds both an activator and a repressor, resulting in constitutively lower transcription. Quantitatively: 4G/4G homozygotes have plasma PAI-1 approximately 25% higher than 5G/5G carriers at baseline, amplifiable to six-fold higher mRNA output under IL-1β stimulation. This amplification under inflammatory challenge is the mechanistically critical feature: the 4G/4G genotype does not merely elevate PAI-1 at baseline, it makes the PAI-1 node hyperresponsive to exactly the inputs — inflammation, metabolic stress, ageing — that drive disease attractor lock-in.

The genotype is therefore an attractor pre-conditioner: it lowers the threshold at which environmental and inflammatory inputs push the regulatory network into PAI-1-dominant

lock-in. In the absence of significant environmental loading (young, healthy, metabolically normal 4G/4G individuals), PAI-1 integrator dominance is not reached. Under the conditions that characterise chronic disease risk — ageing, metabolic syndrome, chronic inflammation, hormonal transitions, cumulative environmental exposures — the 4G/4G background tips the system into lock-in at a lower trigger threshold than equivalent 5G/5G individuals face.

The practical consequence: 4G/4G individuals are not inevitably destined for disease, but when they develop disease in PAI-1-relevant domains, PAI-1 is more likely to be the load-bearing integrator of their disease attractor. Interventions targeting PAI-1 are therefore more likely to be mechanistically load-bearing in 4G/4G patients — which is the pharmacogenomic stratification hypothesis at the heart of this series.

---

3. Cross-Disease Evidence for PAI-1 Integrator Dominance

3.1 Cancer: The Paradox Resolved

PAI-1 is the most extensively validated fibrinolytic prognostic marker in oncology, with ASCO Level 1 evidence for node-negative breast cancer. Its concentration-dependent paradox — elevated tumour PAI-1 predicts poor prognosis yet experimental overexpression inhibits tumour growth — is the most prominent signal in the cancer PAI-1 literature. The RPN framework resolves this paradox: the clinical poor-prognosis signal reflects PAI-1 at physiological-to-moderately-elevated concentrations, where it acts as an integrator maintaining the pro-tumorigenic attractor through angiogenic support and ECM maintenance. The experimental overexpression produces supraphysiological concentrations that cross the concentration-dependent switch threshold into the anti-angiogenic regime, triggering endothelial apoptosis and tumour growth inhibition.

Across prostate, breast, ovarian, and endometrial cancer, the series develops genotype-stratified predictions for aspirin efficacy conditioned on rs1799889 genotype. The ovarian cancer prediction — that aspirin disrupts the platelet-TGF-beta1-PAI-1-PI3K/AKT cisplatin resistance loop in 4G/4G patients, restoring chemosensitivity — is the most clinically urgent. The breast cancer prediction introduces a complexity unique to that cancer type: 4G/4G associates with primary tumour severity while 5G/5G paradoxically associates with lymph node metastasis, generating subtype-specific aspirin predictions that distinguish the RPN account from generic anti-inflammatory hypotheses. The endometrial prediction introduces the three-way genotype × aspirin × metabolic syndrome interaction that most directly tests the attractor pre-conditioning mechanism.

The PAI-1/PD-L1 immune checkpoint connection — PAI-1 drives PD-L1 expression via LRP1/uPAR-dependent JAK-STAT3 signalling — connects the cancer attractor biology to checkpoint inhibitor response. 4G/4G patients are predicted to have higher baseline tumour PD-L1 driven by PAI-1, predicting lower baseline checkpoint inhibitor response and greater benefit from combining checkpoint blockade with PAI-1 reduction.

3.2 Alzheimer's Disease: The Double Lock

The PAI-1/plasmin/pro-BDNF axis provides the neuroplasticity mechanism of AD attractor lock-in. Elevated PAI-1 suppresses plasmin, blocking pro-BDNF cleavage to mature mBDNF and shifting BDNF signalling from synaptic survival (TrkB) toward neuronal apoptosis (p75NTR). The PAI-1/BDNF ratio is elevated 40% above controls in AD patients and inversely correlates with MMSE scores — a quantitative attractor depth metric that is more mechanistically proximate than amyloid burden or tau staging.

Astrocyte senescence, driven and perpetuated by PAI-1 through the SASP, constitutes the self-reinforcing cellular lock-in mechanism: elevated PAI-1 induces astrocyte senescence; senescent astrocytes secrete additional PAI-1 and inflammatory cytokines; the expanding senescent population further amplifies PAI-1 production. The system is self-sustaining once established.

The 4G/4G × APOE4 double lock is the most clinically significant genetic finding in the series. APOE4 expression in brain endothelial cells produces higher Abeta secretion, elevated VWF, and impaired cerebrovascular integrity — all converging on the PAI-1 integrator through platelet activation and inflammatory cytokine production. Meta-analyses report odds ratios for AD in women carrying both 4G/4G and APOE4 as high as 20.8 — a risk magnitude comparable to BRCA1 for breast cancer, currently outside all clinical AD risk stratification protocols. The post-menopausal loss of oestrogen-mediated PAI-1 suppression provides a third input in women, explaining the female AD prevalence excess after age 75.

3.3 COVID-19 and Long COVID: The Biphasic LL-37 Mechanism

The COVID-19 paper introduces the most dynamic account in the series: a three-phase model of genotype-conditioned innate immune failure. Phase 1 — chronic PAI-1 elevation in high-risk comorbid individuals suppresses plasmin, which suppresses LL-37 induction, impairing innate antiviral defence and permitting uncontrolled early SARS-CoV-2 replication. Phase 2 — high viral load drives compensatory IL-1β and TNF-α surge; in 4G/4G carriers this activates the six-fold PAI-1 amplification; simultaneously delayed LL-37 induction at high levels attacks the spike protein and reduces viral burden but in the established cytokine storm context generates the sepsis-like inflammatory catastrophe that characterises severe COVID-19. Phase 3 — rising plasmin from viral clearance begins moderating the cytokine storm but PAI-1 counter-elevation in 4G/4G carriers blunts resolution, producing oscillatory dynamics and persistent endotheliopathy.

Long COVID is framed as the residual PAI-1-dominant attractor state: persistent fibrinolytic suppression, microclot formation, and the same pro-BDNF maturation deficit identified in Alzheimer's disease explaining Long COVID cognitive impairment. The prediction that Long COVID microclot burden correlates with rs1799889 genotype is testable in existing Long COVID biobank samples using published microclot detection methodology.

The convergence of the COVID-19 severe risk profile — obesity, diabetes, age, metabolic syndrome — with the PAI-1-elevating comorbidity list is the strongest epidemiological support in the series for the cross-disease integrator hypothesis. These conditions share no direct immunological mechanism yet all predispose to the same PAI-1-dominant Phase 1 vulnerability.

3.4 Idiopathic Pulmonary Fibrosis: The Persistent Wound State

IPF provides the clearest demonstration of PAI-1's role as a stabilisation hub rather than a root cause. The canonical IPF drivers — TGF-beta1, mechanical stiffness, telomere shortening — are initiating inputs to the fibrotic attractor. PAI-1 is the lock that prevents exit: simultaneously inhibiting ECM degradation through plasmin suppression, maintaining TGF-beta signalling through the same mechanism, and reinforcing ATII cell senescence through the PAI-1/proteasome/p53 molecular brake — a non-proteolytic mechanism where PAI-1 directly binds proteasome components to prevent p53 degradation, locking ATII cells in permanent growth arrest independently of DNA damage signals.

This molecular brake is the most mechanistically specific finding in the series. The non-proteolytic PAI-1/proteasome/p53 interaction provides a self-reinforcing ATII senescence mechanism that standard senolytics address at the cellular level but cannot prevent from re-establishing as long as PAI-1 remains elevated. This generates the cross-series combination prediction in its most specific form: senolytics + PAI-1 modulation is specifically superior to either agent alone in 4G/4G patients because PAI-1 elevation continuously re-drives the proteasomal p53 stabilisation that senolytic clearance temporarily interrupts.

The 4G/4G genotype acts as a susceptibility amplifier in IPF, lowering the lock-in threshold under cigarette smoke and respiratory infection triggers, explaining the heterogeneous progression rates that have frustrated clinical prognostication. Current standard-of-care agents decelerate but do not halt progression because they target initiating inputs without addressing the PAI-1 stabilisation hub — consistent with the attractor framework's prediction that single-node upstream targeting cannot reverse an established multi-node attractor.

3.5 Bacterial Vaccination and Trained Immunity: Re-Permitting the Integrator

Bacterial vaccination and immunostimulation introduce a distinct intervention logic not present in pharmacological approaches: the possibility of epigenetic reprogramming of the PAI-1 node through trained immunity. TLR signalling via LPS and other bacterial products induces gene-specific chromatin modifications — histone H3K4 trimethylation — at the promoters of immune-regulatory genes including PAI-1, potentially shifting the node from a constitutively locked high-expression state to a regulated, inducible state. This is attractor re-permitting rather than attractor disruption: restoring the network's ability to return to the healthy attractor basin rather than forcing it there.

Coley's toxins — bacterial filtrates used empirically in 1890s cancer treatment — are reframed in the RPN series as early demonstrations of multivariate attractor perturbation predating the mechanistic vocabulary. Their variable and unpredictable clinical responses are consistent with the attractor model: efficacy depends on the patient's specific attractor configuration, which varies by genotype and disease stage.

The counterintuitive prediction of the vaccination section is among the most novel in the series: controlled bacterial vaccination in 4G/4G patients may produce a larger PAI-1 spike that, if sufficient to cross the concentration-dependent switch threshold into the anti-angiogenic/anti-tumorigenic regime, produces a paradoxically superior anti-tumour response. BCG bladder cancer efficacy has never been stratified by rs1799889 genotype. The PAI-1/PD-L1 axis adds a second mechanism: 4G/4G patients' higher baseline PAI-1-driven PD-L1 impairs vaccine-induced T cell responses, predicting that vaccination plus PAI-1 reduction (aspirin) plus checkpoint blockade is a rational triple combination specifically in 4G/4G patients.

---

4. Cross-Disease Structural Patterns and Their Implications

4.1 The Staging Prediction Applies Universally

Across all six disease domains, the RPN framework generates the same staging-dependent intervention prediction: single-agent PAI-1 modulation is sufficient at the pre-clinical or early prodromal stage; multi-component combination therapy is required in established disease. In cancer, pre-diagnostic aspirin shows stronger genotype-stratified benefit than post-diagnostic use. In Alzheimer's disease, aspirin and statins show cognitive protection in MCI but not in established moderate-to-severe AD. In COVID-19, early aspirin in 4G/4G patients is predicted to attenuate Phase 2 severity; late intervention in established cytokine storm is insufficient alone. In IPF, PAI-1 modulation may prevent lock-in but cannot reverse it without senolytic co-targeting once the ATII senescent population is established.

This universal staging pattern is a strong prediction of the attractor framework that distinguishes it from disease-specific hypotheses. If staging-dependent efficacy is observed across all domains in genotype-stratified analyses, it constitutes strong cross-domain validation of the framework. If it is absent in any domain, the framework's account of that domain requires revision.

4.2 The Senescence Loop Appears Across All Domains

The PAI-1/senescence/SASP feedback loop is identified in every disease domain in the series: ATII senescence in IPF, astrocyte senescence in AD, tumour microenvironment senescence in cancer, endothelial senescence in COVID-19 endotheliopathy and Long COVID. The cellular substrate of attractor lock-in is consistently a PAI-1-driven senescent cell population that secretes additional PAI-1 in its SASP, maintaining integrator dominance independently of the initiating environmental trigger.

This convergence generates a cross-domain combination therapy prediction: senolytics + PAI-1 modulation is superior to either agent alone across all disease domains where PAI-1-driven senescence is established. The specific agents differ by disease context — dasatinib/quercetin in IPF and AD, navitoclax in cancer — but the structural logic is identical. A clinical programme testing this combination across multiple diseases simultaneously in genotype-stratified populations would be highly informative.

4.3 The Double and Triple Lock Patterns

Several disease contexts generate compound genotype-environment interactions that amplify attractor lock-in beyond the individual contributions of each factor. The APOE4 × 4G/4G double lock in AD (OR 20.8 in women) is the most extreme example in the series. The obesity × 4G/4G interaction in COVID-19 severity, the cigarette smoke × 4G/4G interaction in IPF progression, and the metabolic syndrome × 4G/4G interaction in endometrial cancer all represent the same structural pattern: two independent PAI-1-loading inputs converging on the integrator node in a genetically pre-conditioned system.

The post-menopausal oestrogen withdrawal × 4G/4G interaction appears in both AD and IPF, connecting the female-specific disease burden patterns across both conditions to the same hormonal PAI-1 regulatory mechanism. This predicts that post-menopausal women with 4G/4G genotype represent a high-priority screening subpopulation across multiple disease domains simultaneously — a single genotyping event with implications for cancer prevention, dementia prevention, and fibrotic disease monitoring.

4.4 The Trained Immunity Option as a Complement to Pharmacology

The bacterial vaccination and trained immunity mechanism provides a conceptually distinct intervention route that complements pharmacological PAI-1 modulation. Where aspirin and statins modulate PAI-1 activity continuously, trained immunity epigenetically reprograms the PAI-1 node to restore regulated inducibility — a potentially more durable

intervention whose effects persist after the vaccination stimulus has resolved. The two approaches are predicted to be synergistic: vaccination to restore regulation, followed by aspirin or statin to maintain the modulated state against the chronic environmental inputs that would otherwise re-establish lock-in.

The hygiene hypothesis reinterpretation — reduced lifetime microbial stimulation reducing epigenetic re-permitting of the PAI-1 node in industrialised populations — generates a testable epidemiological prediction distinguishable from standard hygiene hypothesis accounts. If PAI-1 genotype moderates the association between lifetime microbial exposure and disease risk, with the protective effect of microbial exposure concentrated in 4G/4G individuals, this would constitute population-level evidence for the trained immunity mechanism operating through PAI-1.

---

5. Unified Testable Predictions

5.1 UK Biobank Primary Analyses

The UK Biobank contains all variables required for simultaneous testing of the primary prediction across all disease domains: rs1799889 genotyping on approximately 500,000 participants; longitudinal primary care aspirin and statin records; cancer registry linkage for prostate, breast, ovarian, and endometrial cancer; dementia registry linkage; COVID-19 hospitalisation and mortality linkage; and metabolic, lifestyle, and residential history variables for comorbidity adjustment and interaction testing.

Cancer Analysis:

Aspirin x 4G/4G interaction on cancer-specific mortality, separately for prostate (primary prediction: HR interaction significant, benefit in 4G/4G), breast (TNBC subtype interaction), ovarian (chemosensitisation signal in PAI-1-expressing tumours), and endometrial (three-way genotype x aspirin x metabolic syndrome interaction).

Dementia Analysis:

Aspirin x 4G/4G interaction on dementia incidence (primary) and cognitive decline (secondary). APOE4 x 4G/4G interaction on dementia risk testing the double lock (prediction: super-additive risk). Sex x 4G/4G x menopausal status interaction testing the triple input prediction in women.

COVID-19 Analysis:

rs1799889 genotype x comorbidity interaction on COVID-19 hospitalisation and mortality outcomes. Aspirin x 4G/4G interaction in COVID-19 hospitalised patients testing early intervention prediction.

Cross-Disease Coherence Test:

The aspirin x 4G/4G interaction should be simultaneously detectable on cancer-specific mortality and dementia incidence in the same dataset. Concordance across disease domains is a strong validation of the universal integrator hypothesis; domain-specific divergence requires mechanistic explanation.

5.2 Disease-Specific Validation Priorities

Highest clinical urgency — Ovarian cancer chemosensitisation:

A small prospective pilot of aspirin co-administration with carboplatin/paclitaxel in newly diagnosed HGSOC, stratified by rs1799889 genotype and tumour PAI-1 expression. The 5-year survival of 30% unchanged for two decades makes this the most urgent prospective test in the series.

Highest novelty — BCG bladder cancer genotype stratification:

Retrospective genotyping of rs1799889 in archived DNA from BCG-treated bladder cancer registries. BCG efficacy has never been stratified by PAI-1 genotype. This would be the first test of the trained immunity/vaccination prediction.

Highest clinical impact if confirmed — AD double lock:

APOE4 x 4G/4G risk confirmation in a pre-specified analysis of an existing AD cohort. An OR of 20.8 in women has potential clinical implications for genetic risk counselling analogous to BRCA1 screening.

Most immediately testable — Long COVID microclots:

Microclot detection in existing Long COVID biobank samples already genotyped or genotypable for rs1799889. Published methodology, existing samples, straightforward analysis.

Most mechanistically novel — IPF PAI-1/proteasome/p53:

Immunoprecipitation studies in IPF lung tissue to confirm PAI-1 binding to proteasome components and demonstrate p53 stabilisation specifically attributable to this interaction, independent of DNA damage signals.

5.3 Universal Falsification Criteria

The unified RPN-PAI-1 framework is falsified at the series level if any of the following is demonstrated in adequately powered analyses:

The aspirin x rs1799889 genotype interaction is non-significant across all cancer types in UK Biobank analysis, indicating that genotype does not condition aspirin efficacy in any PAI-1-relevant cancer domain.

The APOE4 x 4G/4G interaction on AD risk does not exceed the additive combination of individual risk factors, indicating that the two inputs do not synergistically load the PAI-1 integrator as predicted.

rs1799889 genotype does not predict COVID-19 severity outcomes independently of established comorbidities, indicating that the genetic PAI-1 pre-conditioning is not a significant independent risk factor.

PAI-1 expression in IPF lung tissue does not show evidence of the proteasome-binding p53 stabilisation mechanism, indicating that this molecular brake is not operative as proposed.

Senolytics show equivalent sustained benefit in 4G/4G and 5G/5G IPF or AD patients without PAI-1 co-targeting, indicating that PAI-1-driven senescence reinduction is not the mechanism of senolytic effect attenuation in 4G/4G carriers.

---

6. The Repurposed Drug Landscape

The RPN framework identifies a coherent repurposed drug strategy that follows directly from the integrator node logic: PAI-1-modulating agents with established safety profiles, deployed in genotype-stratified populations, at disease stages where single-node perturbation is sufficient for attractor exit. The same agents recur across all disease domains because they target the same integrator:

Aspirin:

Reduces PAI-1 through NF-kB inhibition and anti-platelet activity. The primary candidate across cancer prevention and treatment, COVID-19 early phase intervention, AD prevention in MCI, and IPF deceleration. Efficacy predicted to be concentrated in 4G/4G carriers across all domains. The RECOVERY trial aspirin arm, multiple cancer aspirin trials, and the VITACOG and similar AD trials all contain data amenable to retrospective genotype-stratified re-analysis.

Statins:

Reduce PAI-1 through RhoA/ROCK inhibition and NF-kB modulation. Independent evidence for PAI-1 reduction, anti-fibrotic properties in IPF models, and cognitive protection signals in observational data. Complementary to aspirin in multi-component intervention strategies. Genotype-stratified re-analysis of existing statin cohort data across all disease domains is the immediate analytical priority.

Senolytics (dasatinib/quercetin, navitoclax):

Address the cellular substrate of attractor lock-in — the senescent cell populations that perpetuate SASP-driven PAI-1 elevation. Required for established disease in IPF and AD; relevant in the tumour microenvironment for cancer. Predicted to show superior sustained benefit in combination with PAI-1 modulation in 4G/4G carriers.

PAI-1 inhibitors (TM5441, tiplaxtinin):

Direct PAI-1 inhibition is the most mechanistically precise intervention. Currently in preclinical development for fibrosis and cancer. The genotype-stratified prediction framework developed in this series provides the patient selection logic for clinical development: 4G/4G carriers across multiple disease domains are the population in whom clinical trials of direct PAI-1 inhibition would be most likely to show significant effects.

Bacterial vaccination / BCG:

Trained immunity-based epigenetic re-permitting of the PAI-1 node. Most advanced clinical data in bladder cancer (intravesical BCG) and respiratory infection prevention (VPM1002). Predicted to show genotype-conditioned effects through both the PAI-1 amplitude mechanism and the PAI-1/PD-L1 immune evasion axis.

---

7. Discussion: What the Cross-Disease Coherence Means

The most important implication of the cross-disease convergence documented in this series is not that PAI-1 causes all these diseases — it does not. The initiating pathologies are distinct: oncogenic mutations in cancer, amyloid and tau pathology in AD, SARS-CoV-2 viral entry in COVID-19, abnormal wound healing in IPF. What PAI-1 integrator dominance explains is why these diseases become progressive, treatment-resistant, and clinically severe — the stabilisation dynamics that prevent resolution despite the body's inherent healing capacity and despite pharmacological intervention.

This distinction matters for how the framework should be tested and applied. The RPN framework is not a competing hypothesis to the amyloid cascade, TGF-beta fibrosis model, or viral cytopathic COVID-19 account. It is a systems-level overlay that explains why these pathologies become locked attractor states rather than self-resolving injury responses. Failure of the PAI-1 integrator hypothesis in any domain does not validate the single-pathway canonical account of that disease — it simply means the stabilisation hub is elsewhere.

The OR of 20.8 for AD in women carrying 4G/4G and APOE4 deserves particular emphasis. If this figure is replicated in pre-specified analyses of independent AD cohorts, it represents a genetic risk combination of clinical significance comparable to the highest-penetrance hereditary cancer syndromes. The absence of this combination from current clinical AD risk stratification — despite both alleles being individually well-characterised — reflects the field's focus on individual genetic risk factors rather than on the interaction effects that the RPN framework predicts. A simple genotyping protocol for rs1799889 alongside existing APOE4 testing in at-risk individuals, particularly post-menopausal women with metabolic syndrome, would have immediate clinical utility if the interaction effect is confirmed.

The COVID-19 application demonstrates the framework's dynamic range: it applies not just to slowly evolving chronic diseases but to acute-on-chronic pathology where the timing of integrator-mediated immune dysregulation determines clinical trajectory within days. The Phase 1/Phase 2/Phase 3 model is a different kind of prediction from the chronic disease attractor predictions — it is a temporal dynamics prediction that requires longitudinal biomarker data to test rather than cohort outcome analysis. This makes it the hardest prediction in the series to test in existing data and the most informative if confirmed.

Finally, the trained immunity and bacterial vaccination thread connects this series to a broader argument about preventive medicine. The hygiene hypothesis, reformulated through the lens of epigenetic PAI-1 regulation, predicts that reduced lifetime microbial stimulation leaves the PAI-1 node without the periodic epigenetic re-permitting that recurrent TLR stimulation provides. The consequence — a chronically upward-drifting PAI-1 baseline through ageing in industrialised populations — would explain the increasing prevalence of PAI-1-relevant diseases (AD, IPF, cancer, cardiovascular disease) in exactly the populations with the most sanitised environments. This is a population-level prediction that the framework shares with the hygiene hypothesis but attributes to a specific molecular mechanism that the hygiene hypothesis literature has not previously identified.

8. Current Limitations and Falsification Targets

This section distinguishes what the RPN-PAI-1 framework has established from what it asserts, and identifies the specific evidence that would confirm or falsify its core claims. Transparent acknowledgement of these limits is not a weakness of the framework but a precondition for its scientific utility.

8.1 Attractor Language: Analogy versus Formal Model

The attractor framework is currently employed as a productive conceptual analogy rather than a formal mathematical model. The language of attractor basins, integrator dominance, and lock-in is used to organise observations and generate predictions, but the framework does not yet specify the state variables, dimensionality, or dynamical equations that would constitute a formal attractor model of the regulatory system. This is an acknowledged limitation.

Formalisation would require specifying the key state variables (PAI-1 activity, plasmin generation rate, senescent cell burden, inflammatory cytokine load as a minimum), the feedback equations governing their interactions, and demonstrating computationally that the system admits multiple stable equilibria corresponding to healthy and pathological states. Such a model would generate quantitative predictions about intervention thresholds — how much PAI-1 suppression is required to shift the system from one basin to another — that the current qualitative framework cannot provide.

One empirical prediction, however, follows directly from the attractor claim and is testable without a formal model: if PAI-1 elevation represents a genuine stable attractor, then partial pharmacological suppression should produce rebound — the system should return toward elevated PAI-1 when treatment is withdrawn. If PAI-1 levels do not rebound after aspirin or statin cessation in 4G/4G carriers, the attractor framing for those conditions is not supported. This snap-back prediction is testable in existing pharmacological washout studies and should be treated as a primary mechanistic test of the framework's central claim.

8.2 PAI-1 Hub Status: Co-occurrence versus Network Centrality

The claim that PAI-1 is a high-centrality integrator node — rather than a co-occurring correlate of systemic disease severity — is the load-bearing assertion of this framework. The evidence presented across the series is consistent with hub status but does not conclusively demonstrate it. Elevated PAI-1 co-occurs with chronic inflammation across all domains addressed; chronic inflammation itself co-occurs across all of them. Demonstrating that PAI-1 is upstream and causally load-bearing, rather than a shared downstream marker of inflammatory severity, requires network topology evidence that the current series does not directly provide.

The strongest available evidence for upstream causal status is the 4G/4G genotype effect: a germline variant that elevates PAI-1 constitutively is upstream by definition, and if 4G/4G genotype predicts disease outcomes independently of established inflammatory markers, this supports causal PAI-1 loading rather than inflammatory

co-occurrence. The UK Biobank analyses specified in Section 5 are therefore not only efficacy tests but hub-status tests: genotype-stratified outcome prediction, independent of CRP, IL-6, and other inflammatory markers, would provide the strongest available evidence that PAI-1 is a load-bearing node rather than a passenger.

The OR of 20.8 for Alzheimer's disease in women carrying both APOE4 and 4G/4G is the most extreme quantitative claim in the series. This figure derives from reported meta-analytic data and individual cohort studies, but the confidence interval around multiplicative gene-gene interaction effects in moderate-sized cohorts is typically wide. This estimate should be treated as a hypothesis-generating upper bound pending pre-specified replication in adequately powered independent cohorts, rather than as an established risk magnitude.

8.3 Aspirin and Statins: Stratification Hypotheses, Not Established Precision Medicines

Aspirin and statins are characterised throughout this series as precision medicines for 4G/4G carriers. This framing requires clarification. Both agents affect PAI-1 through documented mechanisms, and the prediction that their efficacy is concentrated in 4G/4G subpopulations is a specific, testable hypothesis. However, "precision medicine" implies validated genotype-stratified efficacy in prospective or adequately powered retrospective analyses. That validation does not currently exist. The series establishes the mechanistic rationale and generates the prediction; it does not establish the precision medicine claim itself.

The most tractable near-term test is retrospective genotype stratification in existing trial datasets. Several large cardiovascular and cancer prevention trials have banked participant DNA: the ASPREE trial (aspirin in older adults), the RECOVERY trial (aspirin in COVID-19), and multiple aspirin cancer prevention cohorts. Retrospective rs1799889 genotyping in these datasets, followed by interaction analysis of genotype × aspirin on primary outcomes, would constitute the first direct test of the stratification hypothesis. If effect size in 4G/4G individuals is not substantially larger than in 5G carriers across these datasets, the precision medicine framing is not supported regardless of the mechanistic plausibility of the PAI-1 pathway.

Additionally, both aspirin and statins carry substantial off-target effects. Presenting them as precision tools is only justified if efficacy genuinely concentrates in 4G/4G and is not attributable to their anti-inflammatory, anti-platelet, or lipid-lowering effects operating independently of PAI-1 modulation. Separating the PAI-1-specific contribution from these parallel mechanisms is a methodological challenge the current series does not resolve. Mediation analyses in genotype-stratified cohorts — testing whether PAI-1 change mediates outcome benefit in 4G/4G but not 5G carriers — are the appropriate analytical approach.

8.4 The Research Programme Implied by These Limitations

The three limitations above define a concrete research programme whose outputs would determine whether the RPN-PAI-1 framework advances to validated predictive

theory or requires fundamental revision: (1) retrospective genotype stratification in existing aspirin and statin trial datasets to test the precision medicine prediction; (2) snap-back studies in pharmacological washout cohorts to test the attractor stability claim; (3) network topology analyses — protein-protein interaction mapping and perturbation experiments — to establish PAI-1 hub status independently of co-occurrence data; and (4) pre-specified replication of the APOE4 × 4G/4G interaction effect in adequately powered independent AD cohorts. The framework makes all four of these feasible with existing data and methods. Their outcomes will determine the scientific standing of the claims made throughout this series.

9. Conclusion

This synthesis presents a unified account of PAI-1 as a universal systemic integrator node whose dominant expression, conditioned by the rs1799889 4G/4G genotype and amplified by metabolic, hormonal, and inflammatory environmental inputs, drives attractor lock-in across cancer, neurodegeneration, acute infection, and fibrotic lung disease. The framework explains the paradoxical clinical behaviour of PAI-1 across disease domains, the systematic failure of single-target therapies in PAI-1-relevant diseases, the heterogeneous and often inconsistent signals from aspirin and statin trials, and the variable responses to bacterial vaccination and checkpoint inhibitor therapy.

The unified clinical message is the same across all domains: genotyping at rs1799889 identifies the subpopulation in whom PAI-1 is the load-bearing integrator of the disease attractor, and in whom aspirin, statins, senolytics, and direct PAI-1 inhibitors are precision medicines rather than population-level interventions. A single genotyping assay — costing less than one dose of any targeted therapy currently in clinical use — enables this stratification across cancer prevention, dementia prevention, COVID-19 risk management, and fibrotic disease monitoring simultaneously.

The predictions of this framework are specific, falsifiable, testable in existing datasets without new trials for most domains, and clinically actionable if confirmed. We invite researchers with access to UK Biobank data, disease-specific registries, and biobank samples to conduct the stratified analyses specified across this series. The complete series is available at the Zenodo RPN repository: [DOI to be inserted]. Priority for all predictions is established by the individual paper publication dates in the repository.

RPN Series Index

Paper 1: PAI-1 Genotype as a Conditioning Variable for Aspirin Efficacy in Prostate Cancer. Zenodo DOI: [to be inserted].

Paper 2: PAI-1 Genotype as a Conditioning Variable for Aspirin Efficacy in Female Reproductive Cancers: Breast, Ovarian, and Endometrial. Zenodo DOI: [to be inserted].

Paper 3: PAI-1 as a Systemic Integrator Node: First Unified RPN Synthesis. Zenodo DOI: [to be inserted].

Paper 4: The PAI-1 Integrator Node in Alzheimer's Disease: Attractor-State Logic, Repurposed Drug Predictions, and the APOE4 Double Lock. Zenodo DOI: [to be inserted].

Paper 5: Biphasic LL-37/PAI-1 Dynamics as the Mechanistic Basis of Severe COVID-19. Zenodo DOI: [to be inserted].

Paper 6: PAI-1 as a High-Centrality Stabilisation Node in Idiopathic Pulmonary Fibrosis. Zenodo DOI: [to be inserted].

Paper 7 (this paper): PAI-1 as a Universal Systemic Integrator Node: Full Series Synthesis. Zenodo DOI: [to be inserted].

Acknowledgements

AI assistance in literature synthesis, hypothesis formalisation, and manuscript preparation was provided by Claude (Anthropic, claude-sonnet-4-6). All intellectual content, the RPN theoretical framework, the integrator node hypothesis, all disease-specific mechanistic accounts, and all scientific claims are the work of the author. The AI contribution is analogous to research assistance and does not constitute authorship under ICMJE criteria.

Conflict of Interest

The author declares no conflict of interest. No funding was received for this work.

Selected References

1. Duffy MJ, et al. uPA and PAI-1 as biomarkers in breast cancer. Breast Cancer Res. 2014;16:428.

2. Placencio VR, DeClerck YA. PAI-1 in cancer: rationale and insight for future therapeutic testing. Cancer Res. 2015;75:2969-74.

3. Wang J, et al. PAI-1 polymorphisms have significant associations with cancer risk, especially feminine cancer. Technol Cancer Res Treat. 2021;20:15330338211037813.

4. Frontiers Immunology. PAI-1 promotes immune evasion by facilitating PD-L1 expression. Front Immunol. 2024;15:1365894.

5. Kwon MJ, et al. PAI-1 promotes cisplatin resistance in ovarian cancer. Cancer Res. 2023;83(7_Suppl):1684.

6. Yin KJ, et al. PAI-1 as a biomarker for Alzheimer's disease. J Alzheimers Dis. 2017.

7. Netea MG, et al. Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011;9:355-61.

8. Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC. Biochem J. 2022;479:537-59.

9. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020;288:518-36.

10. Chambers RC. Role of PAI-1 in the perpetuation of the fibrotic cascade in IPF. Eur Respir Rev. 2008;17:75-82.

11. Gilabert-Estelles J, et al. PAI-1 4G/5G polymorphism and endometrial cancer. Thromb Res. 2011;130:242-7.

12. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19. Lancet. 2022;399:143-51.

13. Manders P, et al. PAI-1 promoter 4G/5G polymorphism in breast cancer: meta-analysis. Thromb Res. 2013;131:e18-24.

14. Hirano D, et al. Impact of aspirin on biochemical recurrence of prostate cancer. Sci Rep. 2025;15:2195.

15. [Author]. RPN Series Papers 1-6. Zenodo. DOI: [to be inserted].

AI Disclosure

This manuscript was developed with the assistance of Claude (Anthropic, claude-sonnet-4-6), which contributed to literature synthesis, hypothesis formalisation, cross-series integration, and manuscript drafting. All intellectual content, the RPN theoretical framework, all disease-specific mechanistic accounts, and all scientific claims are the work of the author. The AI contribution is analogous to research assistance and does not constitute authorship under ICMJE criteria. This disclosure is provided in accordance with emerging journal and repository standards for AI-assisted manuscript preparation.