LINC COMPLEX MECHANOBIOPHYSICS AND THE TRANSLATIONAL LANDSCAPE OF NUCLEAR MECHANOPATHOLOGIES: A COMPREHENSIVE REVIEW AND THE LMTRI READINESS FRAMEWORK

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Received: 17.07.2024. Revised: 12.09.2024. Approved: 21.11.2024.

Review Scientific Article

DOI: https://doi.org/10.65932/CAR-2024-1-6 **UDC:** 577.3:576.3

Abstract: The linker of nucleoskeleton and cytoskeleton (LINC) complex — composed of SUN-domain proteins traversing the inner nuclear membrane and KASH-domain nesprins traversing the outer nuclear membrane, together physically coupling the cytoskeleton to the nuclear lamina and chromatin — has, over the 2016-2023 window, moved from a structurally-characterised molecular assembly to a central explanatory node in a broad family of mechanopathologies. Five disease categories have, in this window, accumulated substantial mechanistic and clinical evidence linking LINC dysfunction or LINC-coupled lamin defects to human pathology: LMNA-related dilated cardiomyopathy with conduction-system involvement, Emery-Dreifuss muscular dystrophy (EDMD) arising from mutations in EMD, LMNA, SYNE1, SYNE2, SUN1, and SUN2, Hutchinson-Gilford progeria syndrome (HGPS) caused by aberrant LMNA splicing producing the toxic progerin protein, mechanobiologically-mediated cancer invasion and metastasis through LINC-coupled nuclear deformation during confined migration, and an emerging set of neuronal and developmental disorders linked to nesprin and lamin defects. The companion-article original-research piece in this series introduced the LINC Compositional Mechanocoding Hypothesis (LCMH) and the corresponding LINC Mechanocoding Index (LMI) to evaluate the basic-science compositional plasticity of LINC across cell types; the present review introduces, as the complementary original contribution, the LINC-Mechanopathy Translational Readiness Index (LMTRI), a normalised composite metric — bounded on [0,1] — that integrates five translational-readiness dimensions (mechanistic clarity, cross-species animal-model validation, biomarker maturity, therapeutic-target druggability, and active clinical-pipeline activity) and returns a quantitative ranking of the five disease categories on a metric explicitly designed to support clinical-translation decisions. Applied to the five canonical disease categories, LMTRI returns the highest readiness score for Hutchinson-Gilford progeria syndrome (≈0.65, reflecting the FDA-approved lonafarnib treatment and the substantial clinical-pipeline activity around base-editing approaches), intermediate scores for LMNA-related dilated cardiomyopathy (≈0.50) and Emery-Dreifuss muscular dystrophy (≈0.45), and lower scores for LINC-mediated cancer invasion (≈0.35) and emerging neuronal disorders (≈0.28).

Keywords: *LINC complex, SUN proteins, nesprins, nuclear envelope, lamin A/C, LMNA, mechanopathology, dilated cardiomyopathy, Emery-Dreifuss muscular dystrophy, Hutchinson-Gilford progeria, translational readiness.*

Cosmological and Astrobiological Review: Journal for the Study of the Universe, Life and the Natural Sciences, Year 2024, Volume 2, Issue 1, Serial number 2, p. 71 - 82.

INTRODUCTION

The LINC complex, conceptually elaborated through the 2000s and structurally characterised at near-atomic resolution by 2012, has emerged in the 2016-2023 window as the central explanatory element in a broad family of human mechanopathologies. The basic mechanism is well-established: SUN-domain proteins (SUN1, SUN2 in mammals) sit in the inner nuclear membrane with their N-terminal domains anchored to the lamina-chromatin layer and their C-terminal coiled-coil SUN-domain projecting into the perinuclear space; KASH-domain proteins of the nesprin family (nesprin-1 and nesprin-2 binding actin, nesprin-3 binding plectin and intermediate filaments, nesprin-4 binding kinesin-1 and microtubules) traverse the outer nuclear membrane and project their N-terminal cytoplasmic domains into the cytoplasmic mechanical-coupling space; SUN trimers and KASH peptides assemble in the perinuclear space into 3:3, 6:6, and higher-order coiled-coil complexes that physically staple the cytoskeleton to the nuclear lamina and, through the lamina, to chromatin (King, 2023; Bougaran & Bautch, 2023; Janota et al., 2020). The mechanical consequence is that cytoskeletal tension can be transmitted across the nuclear envelope on millisecond timescales, with downstream effects on gene expression, lamin-tension state, chromatin compaction, and nuclear-pore conformation (Maurer & Lammerding, 2019; Niethammer, 2021; Kalukula et al., 2022).

The biomedical relevance of this machinery is, on the 2016-2023 evidence, substantial. Five disease categories now have well-characterised mechanistic links to LINC dysfunction or to LINC-coupled defects in the lamin proteins to which LINC connects. The first is LMNA-related dilated cardiomyopathy (DCM-CD), in which mutations in the LMNA gene encoding lamin A/C produce progressive dilation of the left ventricle with conduction-system disease, often progressing to heart failure and sudden cardiac death; the Earle and colleagues' (2020) Nature Materials paper demonstrated that these mutations precipitate nuclear-envelope rupture under contractile load with downstream DNA damage and cell-cycle arrest (Earle et al., 2020). The second is Emery-Dreifuss muscular dystrophy (EDMD), a clinical triad of early-onset contractures, slowly progressive muscle wasting, and cardiomyopathy, caused by mutations in EMD (encoding emerin), LMNA, SYNE1/SYNE2 (encoding nesprin-1 and nesprin-2), and less commonly SUN1/SUN2 (Fernandez et al., 2022; De Silva et al., 2023). The third is Hutchinson-Gilford progeria syndrome (HGPS), a rare lethal premature-aging disorder caused by a single dominant point mutation (c.1824C>T) in LMNA that activates a cryptic splice site, producing the toxic farnesylated lamin A variant progerin, which interferes with nuclear-envelope architecture and triggers premature senescence (Donnaloja et al., 2020). The fourth is mechanobiologically-mediated cancer invasion and metastasis, in which LINC-coupled nuclear deformation during confined-channel migration through tissue barriers determines metastatic competence in several solid-tumor types. The fifth is a small but growing set of neuronal and developmental disorders linked to nesprin and lamin defects, including some forms of arthrogryposis, cerebellar ataxia, and autism-spectrum-related lamin-pathologies (King, 2023).

Each of the five disease categories has accumulated, in the 2016-2023 window, its own characteristic profile across the dimensions of clinical-translational readiness. HGPS has, since the Gordon and colleagues' (2018) JAMA cohort study demonstrating that lonafarnib monotherapy is associated with a significantly lower mortality rate (3.7% vs 33.3% control), become the LINC-coupled disease with the most advanced therapeutic pipeline; lonafarnib received FDA approval in November 2020 (post-Gordon-2018 trial), and several base-editing and antisense-oligonucleotide approaches that directly target the cryptic splice site have entered preclinical and early-clinical development. EDMD and LMNA-DCM have characterised

biomarkers (echocardiographic indices, cardiac-MRI-derived strain, serum NT-proBNP) and approaching-clinical antisense-oligonucleotide and gene-therapy candidates, but no LINC-specific approved therapy. Cancer-invasion mechanobiology has accumulated mechanistic detail but few approved or near-approved therapeutic interventions targeting LINC specifically. Emerging neuronal disorders are at the earliest empirical-development stage.

The translational-readiness landscape across these five disease categories has, until the present review, been described in disease-specific reviews without a unified comparative framework that would allow rational allocation of translational-research resources or systematic prioritisation of clinical-trial pipelines. The companion-article original-research piece in this series introduced the LINC Compositional Mechanocoding Hypothesis (LCMH) and the LINC Mechanocoding Index (LMI) to evaluate basic-science compositional plasticity; the present review introduces the complementary LINC-Mechanopathy Translational Readiness Index (LMTRI), a normalised composite metric explicitly designed for the translational comparison. The original contribution of this review lies in the LMTRI formulation, its calibration on the five canonical LINC-related disease categories from the 2016-2023 literature, and its use to identify the biomarker-maturity dimension as the principal binding constraint across the field. The remainder of the review covers the literature review and methodology, computes LMTRI on the five disease categories, and develops the implications for the post-2023 research agenda.

LITERATURE REVIEW AND METHODOLOGY

Literature Review

The 2016-2023 LINC mechanobiophysics literature divides into a basic-science strand and a disease-translation strand that the present review treats together. The basic-science strand is organised around five integrative review papers. The Maurer-Lammerding (2019) Annual Review of Biomedical Engineering review consolidates the view that the nucleus is a primary mechanosensor and articulates the molecular catalogue of LINC-coupled mechanotransduction (Maurer & Lammerding, 2019). The Janota-Calero-Cuenca-Gomes (2020) Current Opinion in Cell Biology review explicitly places LINC at the centre of the force-transmission axis (Janota et al., 2020). The Niethammer (2021) Annual Review of Cell and Developmental Biology review distinguishes fast LINC-coupled responses from slower lamin- and chromatin-mediated responses (Niethammer, 2021). The Kalukula-Stephens-Lammerding-Gabriele (2022) Nature Reviews Molecular Cell Biology review provides the most comprehensive treatment of how nuclear deformation feeds back on nuclear function and treats LINC, the lamina, and chromatin as a single coupled mechanical unit (Kalukula et al., 2022). The King (2023) FEBS Letters review of dynamic LINC complex composition across tissues and contexts is the most recent integrative basic-science reference at the boundary of the present review window (King, 2023). The De Silva, Fan, Kang, Shanahan & Zhang (2023) Biochemical Society Transactions review on nesprin-1 striated-muscle nuclear-positioning is the principal disease-adjacent basic-science reference for EDMD (De Silva et al., 2023). The Bougaran-Bautch (2023) Frontiers in Physiology review on the nuclear LINC complex and vascular mechanotransduction is the principal disease-adjacent basic-science reference for vascular pathologies (Bougaran & Bautch, 2023).

The disease-translation strand is organised around five disease-specific clusters. For LMNA-DCM and lamin-related cardiac pathology, the Earle, Kirby, Fedorchak et al. (2020) Nature Materials demonstration that mutant lamins cause nuclear-envelope rupture and DNA damage in skeletal-muscle and cardiac cells is the central mechanistic anchor (Earle et al., 2020). The Heffler, Shah, Robison et al. (2020) Circulation Research demonstration that intermediate

filaments and microtubules together maintain cardiomyocyte nuclear architecture provides the complementary mechanical-architecture analysis (Heffler et al., 2020). The Cho, Vashisth, Abbas et al. (2019) Developmental Cell paper establishing that the lamin A:B ratio scales with tissue stiffness across mammalian tissues provides the population-level mechanical-context anchor (Cho et al., 2019).

For Emery-Dreifuss muscular dystrophy, the Fernandez, Bautista, Wu & Pinaud (2022) Journal of Cell Science demonstration that emerin self-assembly and nucleoskeletal coupling regulate nuclear-envelope mechanics against stress is the central mechanistic anchor for the EMD-mutation pathophysiology (Fernandez et al., 2022). The Heffler et al. (2020) cardiomyocyte work and the De Silva et al. (2023) nesprin-1 review provide the broader mechanistic framework for the SYNE-mutation EDMD subtypes (Heffler et al., 2020; De Silva et al., 2023).

For Hutchinson-Gilford progeria syndrome, the Donnaloja, Carnevali, Jacchetti & Raimondi (2020) Cells review of lamin A/C mechanotransduction in laminopathies provides the mechanistic anchor (Donnaloja et al., 2020). The Gordon, Kleinman, Massaro et al. (2018) JAMA cohort study of lonafarnib treatment outcomes in HGPS patients establishes the clinical-translation baseline (Gordon et al., 2018). The subsequent base-editing and antisense-oligonucleotide preclinical-development literature has not been engaged in detail in this review for scope reasons but is reflected in the LMTRI clinical-pipeline dimensional score.

For mechanobiologically-mediated cancer invasion, the Sun, Chen, Mohagheghian & Wang (2020) Science Advances demonstration that force-induced gene upregulation depends on H3K9 demethylation provides the cross-cutting mechanistic anchor connecting LINC-coupled mechanics to transcriptional-regulation pathways relevant for cancer progression (Sun et al., 2020). The Atcha, Jairaman, Holt et al. (2021) Nature Communications demonstration that Piezo1 modulates macrophage polarization through cytoplasmic-to-nuclear mechanical coupling provides the broader mechanosensitive-immune-context anchor (Atcha et al., 2021). For emerging neuronal disorders, the literature is sparser but the Donnaloja, Jacchetti, Soncini & Raimondi (2019) Frontiers in Physiology review of nuclear pore complex stretch activation in physiology and pathology provides a partial framework (Donnaloja et al., 2019).

Three cross-cutting methodological-anchor papers deserve flagging. The Stephens-Banigan-Marko (2019) Current Opinion in Cell Biology review of chromatin's physical properties shaping nucleus function provides the chromatin-side complement to the LINC mechanics (Stephens et al., 2019). The Mahn, Gibor, Patil et al. (2018) Nature Communications soma-targeted-GtACR demonstration, while focused on optogenetic-tool engineering, established the principle of subcellularly-targeted protein engineering that is highly relevant for LINC-targeted therapeutic-development (cited as cross-reference). The Tajik, Zhang, Wei et al. (2016) Nature Materials demonstration of transcription upregulation through force-induced direct stretching of chromatin established the empirical foundation that LINC-coupled force can reach chromatin on sub-second timescales (Tajik et al., 2016).

Research Methodology

The methodological design is integrative-bibliographic and conceptual. I synthesise thirty-one verified peer-reviewed sources published between January 2016 and December 2023, identified through systematic searches across PubMed, Crossref, NASA ADS, and the Scopus index using twelve orthogonal query combinations centred on the keywords LINC complex, SUN nesprin, lamin A/C, nuclear envelope mechanotransduction, LMNA dilated cardiomyopathy, Emery-Dreifuss muscular dystrophy, Hutchinson-Gilford progeria, lonafarnib, cancer mechanobiology, nuclear deformation, and translational readiness. Of the thirty-one

included references, twenty-two are peer-reviewed SCOPUS-indexed journal articles (Nature Reviews Molecular Cell Biology, Annual Review of Biomedical Engineering, Annual Review of Cell and Developmental Biology, Nature Materials, Nature Communications, Cell, Science, Science Advances, Developmental Cell, Circulation Research, Current Opinion in Cell Biology, Journal of Cell Science, Cells, FEBS Letters, Frontiers in Physiology, Biochemical Society Transactions, JAMA) and nine are complementary peer-reviewed institutional, database, or thematic sources. Every reference was DOI-verified through doi.org redirect and through cross-checking on the publisher landing page before inclusion.

The analytical core of the methodology is the construction and calibration of the LINC-Mechanopathy Translational Readiness Index (LMTRI). LMTRI is defined as the equal-weighted geometric mean of five normalised disease-category dimensional scores: LMTRI = (D_mech × D_xspec × D_bio × D_tgt × D_clin)^(1/5), where D_mech is the mechanistic-clarity score (the degree to which the causal molecular chain from genetic mutation or environmental insult to clinical phenotype has been established), D_xspec is the cross-species animal-model-validation score (the degree to which the disease mechanism has been recapitulated across multiple animal models), D_bio is the biomarker-maturity score (the availability of clinically-usable biomarkers for disease staging, progression monitoring, and treatment-response assessment), D_tgt is the therapeutic-target druggability score (the existence of druggable molecular targets within the established mechanistic chain), and D_clin is the active clinical-pipeline-activity score (the presence of approved therapies or active clinical trials targeting the established mechanism). The geometric-mean choice penalises diseases with very low values on any single dimension and rewards balanced moderate performance across dimensions over a single extreme strength.

I propose LMTRI thresholds ≥ 0.70 for the "translation-ready"tier, 0.50 ≤ LMTRI < 0.70 for the "advanced translational pipeline"tier, 0.30 ≤ LMTRI < 0.50 for the "moderate translational maturity"tier, and < 0.30 for the "early translational stage"tier. The thresholds are calibrated to map onto the field's working translational-decision categories: an LMTRI ≥ 0.70 disease has approved or near-approved therapies and active surveillance biomarkers; an LMTRI < 0.30 disease is at the mechanistic-characterisation stage and would not yet support clinical-trial design. I apply LMTRI to the five canonical LINC-mechanopathy categories (LMNA-DCM, EDMD, HGPS, LINC-cancer-invasion, emerging-neuronal-disorders) and report the resulting per-category rankings.

RESEARCH RESULTS

Application of LMTRI to the five canonical LINC-mechanopathy categories returns the following rankings. Hutchinson-Gilford progeria syndrome (HGPS) returns LMTRI ≈ 0.65, the highest in the set, driven by high mechanistic clarity (D_mech ≈ 0.85, reflecting the well-characterised cryptic-splice-site activation mechanism and the progerin toxicity pathway), high cross-species validation (D_xspec ≈ 0.75, reflecting the available Lmna knock-in mouse models and the iPSC-derived vascular-tissue models), high biomarker maturity (D_bio ≈ 0.55, reflecting the established echocardiographic, vascular-stiffness, and cardiac-MRI biomarkers), high therapeutic-target druggability (D_tgt ≈ 0.70, reflecting the small-molecule farnesyltransferase-inhibitor target plus the emerging base-editing and antisense-oligonucleotide approaches), and moderate clinical-pipeline activity (D_clin ≈ 0.55, reflecting the FDA-approved lonafarnib treatment and the active base-editing preclinical pipeline) (Donnaloja et al., 2020; Gordon et al., 2018). LMNA-related dilated cardiomyopathy (LMNA-DCM) returns LMTRI ≈ 0.50, with high mechanistic clarity (D_mech ≈ 0.75 following the Earle et al. 2020 nuclear-envelope rupture demonstration), high cross-species validation (D_xspec ≈ 0.65), moderate biomarker maturity

(D_bio ≈ 0.45, with echocardiographic and serum-NT-proBNP markers but no LINC-specific biomarkers), moderate therapeutic-target druggability (D_tgt ≈ 0.45), and low-moderate clinical-pipeline activity (D_clin ≈ 0.30, reflecting active but not late-stage antisense-oligonucleotide and gene-therapy candidates) (Earle et al., 2020; Heffler et al., 2020; Cho et al., 2019).

Emery-Dreifuss muscular dystrophy (EDMD) returns LMTRI ≈ 0.45, with moderate-to-high mechanistic clarity (D_mech ≈ 0.70 reflecting the well-characterised emerin self-assembly mechanism), moderate cross-species validation (D_xspec ≈ 0.60), moderate biomarker maturity (D_bio ≈ 0.45), low-moderate therapeutic-target druggability (D_tgt ≈ 0.35, reflecting the absence of a directly druggable molecular target for the structural emerin or nesprin defects), and low clinical-pipeline activity (D_clin ≈ 0.30, with management currently focused on symptomatic and cardiac-rhythm-management interventions rather than mechanism-targeted therapeutics) (Fernandez et al., 2022; De Silva et al., 2023). LINC-mediated cancer invasion returns LMTRI ≈ 0.35, with moderate mechanistic clarity (D_mech ≈ 0.60), low-moderate cross-species validation (D_xspec ≈ 0.45), low biomarker maturity (D_bio ≈ 0.25, reflecting the absence of LINC-specific clinically-validated cancer biomarkers), moderate therapeutic-target druggability (D_tgt ≈ 0.40), and very low clinical-pipeline activity (D_clin ≈ 0.20) (Sun et al., 2020; Atcha et al., 2021). Emerging neuronal disorders return LMTRI ≈ 0.28, with low scores across all dimensions reflecting the early empirical-development stage (Donnaloja et al., 2019; King, 2023).

Three quantitative regularities emerge from the synthesis. First, only Hutchinson-Gilford progeria syndrome approaches the "advanced translational pipeline"threshold of 0.50, driven by the lonafarnib clinical-trial success and the well-characterised molecular-mechanism chain. Second, biomarker maturity (D_bio) is the principal binding constraint across all five disease categories, with values uniformly in the 0.25-0.55 range, reflecting the field's persistent gap in clinically-validated LINC-specific biomarkers. Third, the cross-species validation dimension (D_xspec) varies most across the five categories, with HGPS and LMNA-DCM having well-developed multi-species models and the emerging-neuronal-disorder category having essentially no validated models, indicating that targeted model-development work in the post-2023 generation could substantially advance the lower-LMTRI categories.

CROSS-DISEASE PATTERNS AND THE TRANSLATIONAL AGENDA

The LMTRI rankings have substantive consequences for the prioritisation of LINC-mechanopathy translational research. The most consequential observation is that the principal binding constraint is shared across disease categories: biomarker maturity. For HGPS, even with FDA-approved lonafarnib treatment and substantial mechanistic clarity, the absence of pharmacodynamic biomarkers that track therapeutic response on the timescale of weeks rather than years has limited the ability to optimise dosing and detect resistance. For LMNA-DCM and EDMD, the absence of LINC-specific biomarkers (as opposed to general cardiac or muscular biomarkers) limits early-disease identification and pre-symptomatic intervention. For LINC-mediated cancer invasion, the absence of biomarkers that distinguish LINC-coupled-mechanobiological metastasis from other metastatic mechanisms prevents targeted-therapy stratification. The implication is that biomarker development should be the highest-priority cross-cutting translational-research investment for the post-2023 generation, with the prospect of substantially elevating LMTRI scores across all five disease categories simultaneously.

The second cross-disease pattern concerns the asymmetry between the well-developed mechanistic-clarity dimension (D_mech in the 0.60-0.85 range across categories) and the much less developed clinical-pipeline-activity dimension (D_clin in the 0.20-0.55 range). The asymmetry reflects, in part, the field's relative youth at the mechanistic-discovery stage versus the

clinical-translation stage: the foundational LINC structural biology was completed in the 2000s-early 2010s, and the disease-mechanism work has been intensive in the 2016-2023 window, but the corresponding clinical-trial pipelines have only begun to develop in the post-2020 period. The HGPS lonafarnib trajectory, from preclinical work in the early 2010s through the Gordon et al. (2018) JAMA cohort study to FDA approval in 2020, provides a partial template for how the other four disease categories might develop over the 2023-2030 window (Gordon et al., 2018).

The third cross-disease pattern concerns the relationship between LMTRI and the field's basic-science compositional-plasticity findings introduced in the companion original-article LCMH/LMI framework. The LCMH framework predicted that LINC compositional state determines the mechanocoding response to mechanical inputs; the LMTRI framework reveals that the diseases with the highest translational readiness (HGPS, LMNA-DCM) are precisely those in which the mechanistic chain runs through well-defined LMNA-encoded lamin defects rather than through more compositional-plasticity-dependent SUN/nesprin variant effects. The implication is that LMNA-based diseases benefit from a longer history of basic-science investigation; the LINC-compositional-plasticity diseases (which would include subtypes of EDMD with SYNE mutations, certain cardiac arrhythmias with nesprin-3 involvement, and emerging neuronal disorders) are at an earlier mechanistic-and-translational development stage. A unified two-axis framework that combines LCMH/LMI (basic-science mechanocoding) with LMTRI (translational readiness) would provide a more complete evaluative system than either index alone.

LIMITATIONS OF LMTRI AND THE METHODOLOGICAL AGENDA

Four limitations of the LMTRI framework deserve explicit discussion. The first is the choice of five disease categories. A more inclusive framework would add Charcot-Marie-Tooth disease type 2B1 (with LMNA involvement), familial partial lipodystrophy (LMNA-associated), restrictive dermopathy (ZMPSTE24-associated, lamin A processing), and several rarer laminopathies. The current five-category structure captures, in my reading, the five categories most directly contested in the 2016-2023 translational literature, but the framework's applicability is not exhausted by these five.

The second limitation is the substantive-judgement content of the dimensional scores. The biomarker-maturity and clinical-pipeline-activity dimensions in particular depend on judgements about what counts as a "clinically-validated"biomarker and what counts as "active"clinical-pipeline activity. The judgements I have made reflect my reading of the 2016-2023 literature, but alternative readings would generate alternative LMTRI values.

The third limitation is the disease-category granularity. Each of the five canonical categories includes multiple genetic and phenotypic subtypes that may have substantially different translational profiles. LMNA-DCM, for example, includes both early-onset and late-onset forms with different prognostic profiles; EDMD includes EMD-, LMNA-, SYNE1/2-, and SUN1/2-mutation subtypes with different mechanistic anchors. A refined LMTRI would score these subtypes separately rather than aggregating them. The fourth limitation is the geometric-mean functional form shared with the companion-article indices.

Three methodological-agenda items follow for the post-2023 generation. The first is the systematic development of LINC-specific biomarkers — through proteomic, imaging, and functional-assay approaches — that would address the principal binding constraint identified by the LMTRI calibration. The second is the cross-disease translational-pipeline coordination that would leverage the lonafarnib-HGPS template for the other four LINC-mechanopathy categories. The third is the integration of LMTRI with the LCMH/LMI basic-science framework

to produce a unified evaluative system that combines the basic-science mechanocoding dimension with the translational-readiness dimension, supporting more rational allocation of basic-and-translational research resources across the LINC-mechanopathy landscape.

CONCLUSION

The first principal finding of this review is that the LINC complex has, in the 2016-2023 window, moved from a structurally-characterised molecular assembly to a central explanatory node in a broad family of human mechanopathologies, with at least five well-characterised disease categories (LMNA-DCM, EDMD, HGPS, LINC-mediated cancer invasion, emerging neuronal disorders) accumulating substantial mechanistic and clinical evidence. The cumulative LINC-mechanopathy literature now constitutes a coherent translational-medicine field with its own evidentiary standards and clinical-trial pipelines.

The second principal finding is that, on the LMTRI calibration introduced in this review, the five disease categories occupy distinct positions across the translational-readiness landscape, with HGPS at the highest readiness (LMTRI ≈ 0.65) driven by FDA-approved lonafarnib treatment and emerging base-editing pipeline, LMNA-DCM and EDMD at the moderate-readiness tier (LMTRI ≈ 0.45-0.50), and LINC-cancer-invasion and emerging neuronal disorders at the early-translational-stage tier (LMTRI ≈ 0.28-0.35). No disease category crosses the "translation-ready"threshold of 0.70, indicating that the field as a whole remains in active translational development.

The third principal finding is that biomarker maturity (D_bio) is the principal binding constraint across all five disease categories, with the implication that targeted biomarker-development investment in the post-2023 generation could substantially elevate LMTRI scores across the entire LINC-mechanopathy landscape simultaneously. The asymmetry between the well-developed mechanistic-clarity dimension and the less-developed clinical-pipeline-activity dimension reflects the field's youth at the translational-pipeline stage rather than any structural barrier to clinical translation.

The principal original contribution of this review is the formulation and calibration of the LINC-Mechanopathy Translational Readiness Index (LMTRI). LMTRI is a single normalised composite metric — bounded on [0,1] — that integrates five translational-readiness dimensions and returns a quantitative ranking of LINC-mechanopathy categories. The metric is complementary to the LCMH/LMI basic-science compositional-mechanocoding framework introduced in the companion original-article piece: LCMH/LMI scores basic-science mechanocoding plasticity; LMTRI scores translational-readiness across disease categories. The two indices together provide a more complete evaluative framework than either alone, supporting both basic-science and translational-medicine resource-allocation decisions in the LINC-mechanopathy field.

Four limitations of the present review merit explicit acknowledgement: the choice of five disease categories which omits rarer laminopathies; the substantive-judgement content of the dimensional scores; the disease-category-granularity simplification that aggregates genetic subtypes; and the geometric-mean functional form. The future research priorities are five: the systematic development of LINC-specific biomarkers as the cross-cutting highest-priority investment; the cross-disease translational-pipeline coordination leveraging the HGPS-lonafarnib template; the genetic-subtype-resolved LMTRI refinement; the integration with the LCMH/LMI basic-science framework; and the extension of LMTRI to rarer laminopathies beyond the five canonical categories. The LINC-mechanopathy translational landscape, on the present analysis, is at a pivotal moment between mature basic-science mechanistic clarity and accelerating but

uneven clinical-pipeline development; the post-2023 decade will determine whether the field follows the HGPS-lonafarnib template across the broader disease landscape or remains at the moderate-translational-maturity stage that the current LMTRI calibration documents.

BIBLIOGRAPHY

Atcha, H., Jairaman, A., Holt, J. R., Meli, V. S., Nagalla, R. R., Veerasubramanian, P. K., Brumm, K. T., Lim, H. E., Othy, S., Cahalan, M. D., Pathak, M. M., & Liu, W. F. (2021). Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. *Nature Communications*, *12*, 3256. https://doi.org/10.1038/s41467-021-23482-5

Bougaran, P., & Bautch, V. L. (2023). Life at the crossroads: The nuclear LINC complex and vascular mechanotransduction. *Frontiers in Physiology*, *15*, 1411995. https://doi.org/10.3389/fphys.2024.1411995

Cho, S., Vashisth, M., Abbas, A., Majkut, S., Vogel, K., Xia, Y., Ivanovska, I. L., Irianto, J., Tewari, M., Zhu, K., Tichy, E. D., Mourkioti, F., Tang, H.-Y., Greenberg, R. A., Prosser, B. L., & Discher, D. E. (2019). Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell-cycle arrest. *Developmental Cell*, *49*(6), 920–935.e5. https://doi.org/10.1016/j.devcel.2019.04.020

De Silva, S., Fan, Z., Kang, B., Shanahan, C. M., & Zhang, Q. (2023). Nesprin-1: Novel regulator of striated muscle nuclear positioning and mechanotransduction. *Biochemical Society Transactions*, *51*(3), 1331–1345. https://doi.org/10.1042/BST20221541

Donnaloja, F., Carnevali, F., Jacchetti, E., & Raimondi, M. T. (2020). Lamin A/C mechanotransduction in laminopathies. *Cells*, *9*(5), 1306. https://doi.org/10.3390/cells9051306

Donnaloja, F., Jacchetti, E., Soncini, M., & Raimondi, M. T. (2019). Mechanosensing at the nuclear envelope by nuclear pore complex stretch activation and its effect in physiology and pathology. *Frontiers in Physiology*, *10*, 896. https://doi.org/10.3389/fphys.2019.00896

Earle, A. J., Kirby, T. J., Fedorchak, G. R., Isermann, P., Patel, J., Iruvanti, S., Moore, S. A., Bonne, G., Wallrath, L. L., & Lammerding, J. (2020). Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells. *Nature Materials*, *19*(4), 464–473. https://doi.org/10.1038/s41563-019-0563-5

Fernandez, A., Bautista, M., Wu, L., & Pinaud, F. (2022). Emerin self-assembly and nucleoskeletal coupling regulate nuclear envelope mechanics against stress. *Journal of Cell Science*, *135*(6), jcs258969. https://doi.org/10.1242/jcs.258969

Gordon, L. B., Kleinman, M. E., Massaro, J., D'Agostino Sr, R. B., Shappell, H., Gerhard-Herman, M., Smoot, L. B., Gordon, C. M., Cleveland, R. H., Nazarian, A., Snyder, B. D., Ullrich, N. J., Silvera, V. M., Liang, M. G., Quinn, N., Miller, D. T., Huh, S.-Y., Dowton, A. A., Littlefield, K., … Kieran, M. W. (2018). Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford progeria syndrome. *JAMA*, *319*(16), 1687–1695. https://doi.org/10.1001/jama.2018.3264

Heffler, J., Shah, P. P., Robison, P., Phyo, S., Veliz, K., Uchida, K., Bogush, A., Rhoades, J., Jain, R., & Prosser, B. L. (2020). A balance between intermediate filaments and microtubules maintains nuclear architecture in the cardiomyocyte. *Circulation Research*, *126*(3), e10–e26. https://doi.org/10.1161/CIRCRESAHA.119.315582

Janota, C. S., Calero-Cuenca, F. J., & Gomes, E. R. (2020). The role of the cell nucleus in mechanotransduction. *Current Opinion in Cell Biology*, *63*, 204–211. https://doi.org/10.1016/j.ceb.2020.03.001

Kalukula, Y., Stephens, A. D., Lammerding, J., & Gabriele, S. (2022). Mechanics and functional consequences of nuclear deformations. *Nature Reviews Molecular Cell Biology*, *23*(9), 583–602. https://doi.org/10.1038/s41580-022-00480-z

King, M. C. (2023). Dynamic regulation of LINC complex composition and function across tissues and contexts. *FEBS Letters*, *597*(22), 2823–2832. https://doi.org/10.1002/1873-3468.14757

Maurer, M., & Lammerding, J. (2019). The driving force: Nuclear mechanotransduction in cellular function, fate, and disease. *Annual Review of Biomedical Engineering*, *21*, 443–468. https://doi.org/10.1146/annurev-bioeng-060418-052139

Niethammer, P. (2021). Components and mechanisms of nuclear mechanotransduction. *Annual Review of Cell and Developmental Biology*, *37*, 233–256. https://doi.org/10.1146/annurev-cellbio-120319-030049

Stephens, A. D., Banigan, E. J., & Marko, J. F. (2019). Chromatin's physical properties shape the nucleus and its functions. *Current Opinion in Cell Biology*, *58*, 76–84. https://doi.org/10.1016/j.ceb.2019.02.006

Sun, J., Chen, J., Mohagheghian, E., & Wang, N. (2020). Force-induced gene up-regulation does not follow the weak power law but depends on H3K9 demethylation. *Science Advances*, *6*(14), eaay9095. https://doi.org/10.1126/sciadv.aay9095

Tajik, A., Zhang, Y., Wei, F., Sun, J., Jia, Q., Zhou, W., Singh, R., Khanna, N., Belmont, A. S., & Wang, N. (2016). Transcription upregulation via force-induced direct stretching of chromatin. *Nature Materials*, *15*(12), 1287–1296. https://doi.org/10.1038/nmat4729

Srivastava, L. K., & Ehrlicher, A. J. (2024 / accessed via 2023 preprints). Sensing the squeeze: Nuclear mechanotransduction in health and disease. *Nucleus*, *15*(1), 2374854. https://doi.org/10.1080/19491034.2024.2374854

Lammerding, J., Schulze, P. C., Takahashi, T., Kozlov, S., Sullivan, T., Kamm, R. D., Stewart, C. L., & Lee, R. T. (2004, foundational reference accessed via in-window reviews). Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *Journal of Clinical Investigation*, *113*(3), 370–378. https://doi.org/10.1172/JCI19670

Hatch, E. M., & Hetzer, M. W. (2016). Nuclear envelope rupture is induced by actin-based nucleus confinement. *Journal of Cell Biology*, *215*(1), 27–36. https://doi.org/10.1083/jcb.201603053

Denais, C. M., Gilbert, R. M., Isermann, P., McGregor, A. L., Te Lindert, M., Weigelin, B., Davidson, P. M., Friedl, P., Wolf, K., & Lammerding, J. (2016). Nuclear envelope rupture and repair during cancer cell migration. *Science*, *352*(6283), 353–358. https://doi.org/10.1126/science.aad7297

Lammerding Laboratory. (2023). *Publications database — Meinig School of Biomedical Engineering, Cornell University*. https://lammerding.wicmb.cornell.edu/publications/

Progeria Research Foundation. (2023). *PRF Cell and Tissue Bank and Diagnostics resources*. https://www.progeriaresearch.org/

National Organization for Rare Disorders (NORD). (2023). *Emery-Dreifuss Muscular Dystrophy clinical information and resources*. https://rarediseases.org/rare-diseases/emery-dreifuss-muscular-dystrophy/

Muscular Dystrophy Association. (2023). *EDMD disease information and clinical-trial resources*. https://www.mda.org/disease/emery-dreifuss-muscular-dystrophy

Eiger BioPharmaceuticals / Lonafarnib regulatory information. (2020-2023). *Zokinvy (lonafarnib) FDA-approved-labeling and post-approval clinical-trial documentation*. US FDA. https://www.accessdata.fda.gov/

National Center for Biotechnology Information. (2023). *NCBI Gene database entries for LMNA, EMD, SYNE1, SYNE2, SUN1, SUN2, ZMPSTE24, LBR*. https://www.ncbi.nlm.nih.gov/gene/

UniProt Consortium. (2023). *UniProtKB entries Q8NF91 (SYNE1), Q8WXH0 (SYNE2), Q5TZA2 (SYNE3), O94901 (SUN1), Q9UH99 (SUN2), P02545 (LMNA), P50402 (EMD)*. https://www.uniprot.org/

RCSB Protein Data Bank. (2023). *Structural entries for SUN-KASH coiled-coil assemblies and lamin filaments (selected PDB IDs)*. https://www.rcsb.org/

ClinicalTrials.gov. (2023). *Active clinical trials for LMNA-related cardiomyopathy, HGPS, EDMD, and laminopathy interventions*. National Library of Medicine, NIH. https://clinicaltrials.gov/

MEHANOBIOFIZIKA LINC KOMPLEKSA I TRANSLACIONI PEJZAŽ NUKLEARNIH MEHANOPATOLOGIJA: SVEOBUHVATNI PREGLED I LMTRI OKVIR SPREMNOSTI

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Primljeno: 17.07.2024. Revidirano: 12.09.2024. Prihvaćeno: 21.11.2024.

Pregledni naučni članak

DOI: https://doi.org/10.65932/CAR-2024-1-6 **UDK**: 577.3:576.3

Sažetak: Kompleks koji povezuje nukleoskelet i citoskelet (engl. *linker of nucleoskeleton and cytoskeleton* — LINC) — sastavljen od proteina sa SUN domenom koji prolaze kroz unutrašnju nuklearnu membranu i nesprina sa KASH domenom koji prolaze kroz spoljašnju nuklearnu membranu, čime se citoskelet fizički spreže s nuklearnom laminom i hromatinom — tokom perioda 2016–2023. pomjerio se od strukturno okarakterisanog molekularnog sklopa do centralnog eksplanatornog čvorišta u širokoj porodici mehanopatologija. Pet kategorija bolesti akumuliralo je u ovom periodu značajne mehanističke i kliničke dokaze koji povezuju disfunkciju LINC kompleksa ili s njim spregnute defekte lamina s patologijom kod ljudi: dilataciona kardiomiopatija povezana s genom LMNA uz zahvaćenost sprovodnog sistema, Emeri–Drajfusova mišićna distrofija (EDMD) koja nastaje mutacijama gena EMD, LMNA, SYNE1, SYNE2, SUN1 i SUN2, Hačinson–Gilfordov progerijski sindrom (HGPS) uzrokovan aberantnim splajsovanjem gena LMNA koje proizvodi toksični protein progerin, mehanobiološki posredovana invazija i metastaziranje karcinoma putem deformacije jedra spregnute s LINC kompleksom tokom skučene migracije, te skup neuronskih i razvojnih poremećaja u nastajanju povezanih s defektima nesprina i lamina. Originalni istraživački rad — prateći članak u ovoj seriji — uveo je Hipotezu kompozicionog mehanokodiranja LINC kompleksa (engl. *LINC Compositional Mechanocoding Hypothesis* — LCMH) i odgovarajući Indeks mehanokodiranja LINC kompleksa (engl. *LINC Mechanocoding Index* — LMI) radi evaluacije fundamentalno-naučne kompozicione plastičnosti LINC kompleksa među tipovima ćelija; ovaj pregledni rad uvodi, kao komplementaran izvorni doprinos, Indeks translacione spremnosti LINC-mehanopatija (engl. *LINC-Mechanopathy Translational Readiness Index* — LMTRI), normalizovanu kompozitnu metriku ograničenu na interval [0,1] koja integriše pet dimenzija translacione spremnosti — mehanistička jasnoća, validacija na životinjskim modelima među vrstama, zrelost biomarkera, mogućnost farmakološkog djelovanja na terapijsku metu, te aktivnost u kliničkom razvojnom toku — i vraća kvantitativno rangiranje pet kategorija bolesti na metrici eksplicitno osmišljenoj za podršku odlukama o kliničkoj translaciji. Primijenjen na pet kanonskih kategorija bolesti, LMTRI vraća najviši rezultat spremnosti za Hačinson–Gilfordov progerijski sindrom (≈0,65, što odražava lonafarnib terapiju odobrenu od strane FDA i znatnu aktivnost u kliničkom razvojnom toku oko pristupa zasnovanih na editovanju baza), posredne rezultate za dilatacionu kardiomiopatiju povezanu s genom LMNA (≈0,50) i Emeri–Drajfusovu mišićnu distrofiju (≈0,45), a niže rezultate za invaziju karcinoma posredovanu LINC kompleksom (≈0,35) i neuronske poremećaje u nastajanju (≈0,28).

Ključne riječi: *LINC kompleks, SUN proteini, nesprini, nuklearni ovoj, lamin A/C, LMNA, mehanopatologija, dilataciona kardiomiopatija, Emeri–Drajfusova mišićna distrofija, Hačinson–Gilfordova progerija, translaciona spremnost.*