Supplementary Information (SI) for Lab on a Chip.
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Dynamic biomimicry in skin-on-a-chip: Multi-scale construction to translational dermatology, drug screening and cosmetic evaluation

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Table S1. Summary of representative skin-on-a-chip studies across different dynamic levels

Model type /dynamic level	Cells	Matrix / scaffold	Materials	Flow rates	Culture duration	Throughput	Barrier Metrics	Primary application	Limitations / future need	Ref.
Dynamic barrier (Epidermis)	NHKs	PET membrane	PMMA	Medium flow 1 μL/min; air flow 1 μL/min; shear stress 3×10^{-4} dyn/cm^2	2 d submerged + 14 d ALI; monitored to 21 d ALI	24-unit chip	TEER; Cascade Blue/Texas Red permeability; epidermal differentiation markers	Irritation testing; Barrier function	Epidermis-only model with limited multicellular complexity; flow profile and shear stress require further investigation, and more sophisticated biomimetic models with additional irritation biomarkers are needed.	1
Dynamic barrier (Epidermis)	HaCaT	Col I + sponge scaffold	PDMS + PMMA	41.67 μL/h submerged; 30 μL/h lower-channel perfusion during ALI	7 d submerged + 35 d ALI	Single unit	H&E-based stratification and stratum corneum; no TEER/permeability	Barrier function; Tissue engineering	Mainly demonstrated culture feasibility and epidermal morphology; no clear advantage was observed for low-density 2D submerged cultures, and further validation of functional barrier readouts and broader cell/tissue applications is needed.	2
Dynamic barrier (Epidermis)	HaCaT	PET membrane	PDMS	NR	15 d for permeation assay; 5 d for viability assay	24-site format	FITC-dextran permeability across HaCaT monolayer	Drug permeation / PK; Irritation testing	Limited to a HaCaT monolayer-based barrier without full epidermal differentiation; long-term culture robustness and cell-layer integrity need improvement for more reliable kinetic permeation assays.	3
Dynamic barrier (Epidermis); with pigmentation	NHKs + NHMs	PET membrane	PMMA	Medium flow 1 μL/min; air flow 1 μL/min	2 d submerged + 14 d ALI	3-unit chip	Cascade Blue/Texas Red permeability; prednisone acetate permeation; ZO-1/differentiation markers	Barrier function; Cosmetic safety	Epidermis-based model remains limited in multicellular tissue complexity; broader validation with more chemicals, inter-laboratory testing, and expanded high-throughput formats is needed for pharmaceutical and cosmetic applications.	4
Dynamic mechanics (Full-thickness)	HEKs + HDFs	PS scaffold + fibroblast-derived matrix	polycarbonate + PDMS	Dermal perfusion 1.5 μL/min; epidermal perfusion 2 μL/min; air flow 1.5 μL/min	6 d dermis + 2 d submerged + 11 d ALI	Single unit	TEER; FITC-dextran permeability; epidermal stratification and barrier function	Barrier function; Drug testing	Dermal maturation and FDM deposition require careful optimization to avoid keratinocyte infiltration or channel clogging; future work should integrate additional cell types and expand disease- or patient-specific validation.	5
Dynamic mechanics (Full-thickness)	HEKs + HDFs	PS scaffold + fibroblast-derived matrix	PS + PDMS	All at 1.5 μL/min	12 d dermis + 2 d submerged + up to 14 d ALI	Single unit	TEER; lucifer yellow penetration	Barrier function; Irritation testing	Mainly validated as a proof-of-concept barrier-sensing platform; TEER sensitivity depends on electrode geometry and chamber design, and broader validation with diverse barrier tissues and testing scenarios is needed.	6
Dynamic mechanics (Full-thickness)	HaCaT + HDFs	Fibrin gel + PC membrane	vinyl + PMMA + PDMS	lower-channel flow 40 μL/h; keratinocyte seeding 50 μL/min	24 h fibroblast spreading + 6 h keratinocyte attachment	Single unit	Multilayer tissue formation and cell viability by fluorescence/confocal imaging; no TEER/permeability assay	Tissue engineering; Multilayer tissue generation	Proof-of-concept platform mainly demonstrates multilayer tissue generation rather than mature skin barrier function; further epidermal maturation, functional readouts, and mechanical stimulation strategies are needed.	7
Dynamic mechanics (Full-thickness)	HEKs + HDFs	Col I + PET membrane	PDMS	Gravity-driven rocker flow; average shear stress ~0.06 Pa	3 d dermis + 3 d submerged + 11 d ALI	24-unit plate; scalable to 128 units	TEER; dextran permeability; LOR and collagen IV staining	Barrier function; Toxicity screening	Highly scalable platform, but TEER sensitivity remains non-uniform and requires further optimization of electrode integration, frequency range, and electrode geometry; tissue-specific maturation and application validation should be expanded.	8

Model type /dynamic level	Cells	Matrix / scaffold	Materials	Flow rates	Culture duration	Throughput	Barrier Metrics	Primary application	Limitations / future need	Ref.
Dynamic mechanics (Full-thickness)	HaCaT + fibroblasts	Col I + PET membrane	PDMS	Medium flow 1 μL/min; air flow 1 μL/min; shear stress 3×10^{-4} dyn/cm	2 d submerged + day 3–16 ALI	Single unit	TEER; fluorescent molecule permeability; stratum corneum thickness; collagen IV/FLG/LOR	Inflammation / infection; Drug efficacy	The platform remains based on a simplified HaCaT/fibroblast collagen model and a P. acnes/SLS-induced injury setting; future work should incorporate more native skin cell types, optimize dermal stiffness, and expand multi-chamber or high-throughput drug-screening validation.	9
Dynamic mechanics (Full-thickness); with stretch	HEKs + HDFs	Col I	PDMS	10 μL/min; tensile stimulation: 0.01 Hz, 5.3 mm/min	28 d	Single unit	H&E morphology and barrier-related proteins; no TEER/permeability assay	Mechanobiology; Wound-healing-like modeling	Mainly demonstrates tensile-stimulation-induced skin responses rather than a validated disease or drug-testing model; loading parameters and long-term tissue damage need further optimization for damaged-barrier or wound-healing applications.	10
Dynamic mechanics (Full-thickness); with stretch	HEKs + HDFs	Col I + sulfo-SANPAH	PDMS	Gravity-driven operation; mechanical stimulation: 5% compressive strain @ 0.01 Hz, 12 h on/12 h off	5 d dermis + 3 d epidermis + 28 d ALI/mechanical aging	Single unit	H&E epidermal thickness and COL4A/fibronectin/FLG/K10/IVL markers; no TEER/permeability assay	Skin aging model; Cosmetic evaluation	The ageing model remains simpler than native skin because it is limited by current fibroblast–keratinocyte co-culture conditions; future studies should add immune cells, capillaries, peripheral nerves, hair follicles, and sweat glands for more physiologically complete ageing models.	11
Dynamic mechanics (Full-thickness); with stretch	HEKs + HDFs	Col I + porous membrane	PDMS	NR; Stretching: 10% strain @ 0.01 or 0.05 Hz; 12 h/day	4 d fibroblasts + 4 d keratinocytes + 7 d ALI/stretch	Single unit	H&E morphology, stratum corneum thinning, and collagen IV/fibronectin/K10 markers; no TEER/permeability	Anti-wrinkle evaluation; Mechanobiology	The model establishes wrinkle-like morphology under rapid cyclic stretching but remains an early ageing-mimic platform; stretch frequency and strain require careful optimization because higher-frequency stimulation can damage epidermal and dermal structures.	12
Dynamic mechanics (Full-thickness); with stretch	HEKs + HDFs + HUVECs	Col I with hollow vascular channels	PDMS + Ecoflex + 3D-printed resin	Perfusion 2–3 mL/h; Stretching: 10% strain @ 0.05 Hz	2 d dermis + 2 d endothelialization + 3 d ALI + 4 d stretch	Single unit	Epidermal capacitance measurement; epidermal thickness/stratification; collagen IV and Ki67 staining	Mechanobiology; Transdermal testing	Mainly demonstrates that combined perfusion and dynamic stretching can improve skin-equivalent morphology; further optimization of perfusion/stretching parameters and validation of barrier function, disease modelling, and drug-testing applications are needed.	13
Dynamic circulation (immune)	Dermal fibroblasts + HUVECs + M1/M2 macrophages	Matrigel + collagen/fibronectin coating	PDMS	NR	24-48 h	Single unit	NR	Wound healing; Immune response modeling	The model captures the paracrine component of early wound inflammation but does not reconstruct a full-thickness epidermal barrier or all wound-healing stages; future work should incorporate additional cell types and extend the platform to later proliferation and remodelling phases	14
Dynamic circulation (Vascularized &immune)	HDFs + HaCaT + HUVECs + HL-60	Col I + porous membrane	PDMS	10 μL/min	7 d dermis + 3 d HaCaT stabilization + 7–10 d differentiation	Single unit	Epidermal differentiation: K5/FLG; endothelial barrier: 70 kDa FITC-dextran permeability and CD31	Immune response modeling; Irritation testing	The vascularized skin chip recapitulates leukocyte recruitment after UV stimulation, but vascular permeability was higher than in Transwell and endothelial differentiation was partly affected by chip culture conditions; further optimization of medium compatibility, endothelial stability, and disease-specific immune validation is needed.	15
Dynamic circulation (Vascularized &immune)	HEKs + HDFs + dermal microvascular endothelial cells + primary neutrophils	Col I	PMMA/glass	Gravity-driven microvascular perfusion; flow rate NR	2 d endothelialization + 2 d keratinocyte confluence + 7–10 d ALI;	Single unit	Epidermal markers: K14/K10/FLG/LOR/IVL; endothelial barrier: 40 kDa FITC-dextran permeability and CD31/VE-cadherin	Inflammation / infection; Immune response modeling	The model is limited by mixed-origin commercial primary cells and lacks skin-resident immune components; next-generation platforms should use autologous cellular components and incorporate tissue-resident immune cells to model adaptive immunity and personalized HSV responses.	16

Model type /dynamic level	Cells	Matrix / scaffold	Materials	Flow rates	Culture duration	Throughput	Barrier Metrics	Primary application	Limitations / future need	Ref.
Dynamic circulation (Vascularized &immune)	HEKs + HDFs + HUVECs + HL-60	Porous scaffold + Col I	NR	Gravity-driven perfusion; flow rate NR	Long-term ALI culture	Single unit	No TEER/permeability assay; stratum corneum/epidermal thickness and FLG/IVL/LOR markers; CD31/CD144 and microsphere perfusion	Inflammation / immune response modeling; Drug testing	Although the platform improves contraction control and vascularized AD-like modelling, pericyte incorporation, stepwise higher-shear maturation, broader cytokeratin/stromal marker panels, and validation with primary immune subsets and disease-specific therapeutic benchmarks are still needed.	17
Dynamic circulation (Vascularized)	HaCaT + HS27 + HUVECs	Fibronectin-coated PET membranes (0.4 μm)	PDMS	Gravity-driven perfusion; flow rate NR	3 d to confluence; up to 3 weeks culture stability	Single unit	Endothelial barrier: ZO-1 and 4 kDa FITC-dextran permeability	Inflammation / infection; Drug testing	The model simulates TNF-α-induced inflammation and edema but remains based on simplified monolayer cell layers using HaCaT, fibroblasts, and HUVECs; future work should improve epidermal maturation, immune-cell integration, and broader drug or irritant validation.	18
Dynamic circulation (Vascularized)	HDFs + HEKs / HaCaT; HUVECs	Col I + PC membrane	PDMS	Gravity-driven perfusion; 10 μL/min	5-7 d fibroblasts + 2 d keratinocytes + 5-10 d ALI	Single unit	H&E stratification and K5/IVL/FLG markers; no TEER/permeability assay	Barrier function; Tissue engineering	Mainly establishes on-chip skin construction and perfusion-dependent cell viability; collagen contraction, gel thickness-dependent nutrient limitation, and lack of immune-function validation remain to be further improved for physiological skin modelling.	19
Dynamic circulation (Vascularized)	HaCaT + Hs27 fibroblasts + HUVECs	Porous membranes	PDMS	Gravity-driven perfusion; flow rate NR	3 d to confluence + 42 h post-exposure	Single unit	MTT viability and ZO-1 tight-junction ratio; no TEER/permeability assay	Irritation testing; Toxicity screening	The dual-parameter model improves irritation prediction by combining cell viability and endothelial tight-junction disruption, but validation remains limited to 20 reference substances; more chemicals, human patch-test datasets, and standardized inter-laboratory testing are needed.	20
Dynamic circulation (Vascularized)	HDFs + HEKs + HUVECs	Fibrin gel	PDMS	NR	6 d total (2 d pre-culture + 4 d treatment)	Single unit	Claudin-1/K14 and live/dead staining for keratinocyte integrity; no TEER/permeability assay	Irritation testing; Cosmetic safety	Proof-of-concept irritation model based on angiogenic responses rather than a mature full-thickness epidermal barrier; broader validation with diverse irritants, allergens, corrosives, and standardized quantitative biomarkers is needed for cosmetics and drug-safety testing.	21
Dynamic circulation (Vascularized)	N/TERT keratinocytes + HCA2 fibroblasts + HUVECs + pericytes	Fibrin + Col I/Matrigel	PDMS	NR	4 d vascularization + 14 d skin culture	Single unit	No TEER/permeability assay; epidermal stratification and laminin 332/K14/IVL/TGM1 markers; 70 kDa FITC-dextran vascular perfusability	Drug testing; Vascularized skin equivalent	The model improves vascularized skin-equivalent construction, but epidermal maturation under ALI remains limited and the tissue is less stratified than native skin; future work should optimize nutrient transport, topical/systemic delivery assays, and scalable multi-chip formats for higher-throughput therapeutic testing.	22
Systemic dynamics (Multi-organ)	HEKs + hNSC-derived neurons / hiPSC-HEPs	Col I	PDMS	NR	3 d stabilization + ALI to day 7	6-unit chip	Cornified epidermis with IVL/CK10/CK5 markers; no TEER/permeability assay	Toxicity screening; multi-organ toxicity	The platform enables skin–nerve and skin–liver coupling, but remains a proof-of-concept system with a simplified epidermal barrier and limited test compounds; broader chemical validation, quantitative barrier/permeation assessment, and standardized screening workflows are needed.	23

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Systemic dynamics (Multi-organ)	iPSC-cardiomyocytes + primary hepatocytes	Strat-M membrane	PMMA + PDMS	Rocker-driven; flow rate NR	Acute 3 d; chronic topical 10 d	Single unit	Strat-M membrane drug permeation by LC-MS/MS; no living skin barrier metrics	Drug permeation/ PK; multi-organ toxicity	The system links dermal absorption to heart–liver toxicity, but uses a synthetic Strat-M skin surrogate rather than a living skin equivalent; future work should incorporate biological skin barriers, skin heterogeneity, and broader pharmacokinetic validation of topical drug delivery.	24
Systemic dynamics (Multi-organ)	Caco-2 + HEKs + gut microbes	PET membrane + PC membrane	PC	Gravity-driven perfusion; 15° tilt, 500 s interval	14 d gut differentiation + skin ALI differentiation	Single unit	Gut barrier: TEER, 70 kDa FITC-dextran permeability, and ZO-1; reconstructed epidermis: H&E and K5/IVL/FLG/Ki67 markers.	Gut–skin axis modeling; Inflammation / infection	The chip captures gut microbiota–skin crosstalk, but relies on Caco-2 cells and lacks immune components; future iterations should incorporate primary or patient-derived intestinal/skin cells, immune cells, and broader microbiome or disease-specific validation.	25
Systemic dynamics (Multi-organ)	*Ex vivo* human epidermis + KGN or TM3 aggregates	*Ex vivo* epidermis	PDMS	NR	48 h aggregate formation + 24 h stimulation	Single unit	H&E epidermal structure and stratum corneum thickness; no TEER/permeability assay	Cosmetic safety; Hormone crosstalk model	Sex-hormone regulation is modelled mainly through local hormone gradients without vascular delivery, limiting systemic hormone distribution and vascular–epidermal interactions; future work should incorporate vascular structures and broader donor or hormone-condition validation.	26

PMMA: polymethyl methacrylate; PDMS: polydimethylsiloxane; PS: polystyrene; PC: polycarbonate; PET: polyethylene terephthalate; HEKs: human epidermal keratinocytes; HDFs: human dermal fibroblasts; HUVECs: human umbilical vein endothelial cells; Col I: type I collagen; ALI: air-liquid interface; TEER: transepithelial electrical resistance; FLG: filaggrin; IVL: involucrin; LOR: loricrin; NR: not reported.

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