The Industrialization of Rare Disease Drug Discovery

September 13th, 2017

Chris Gibson
Co-Founder and CEO
Recursion Pharmaceuticals

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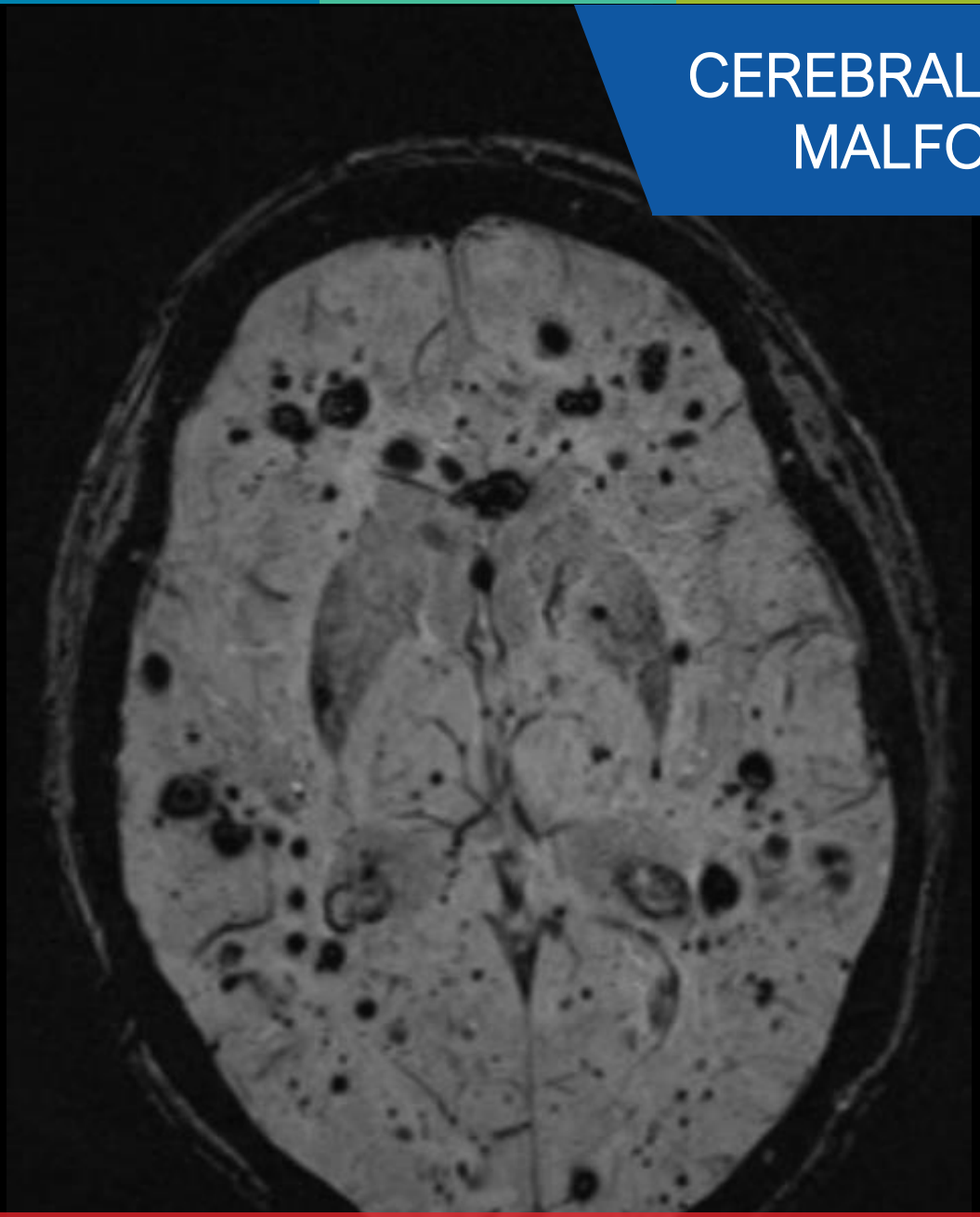
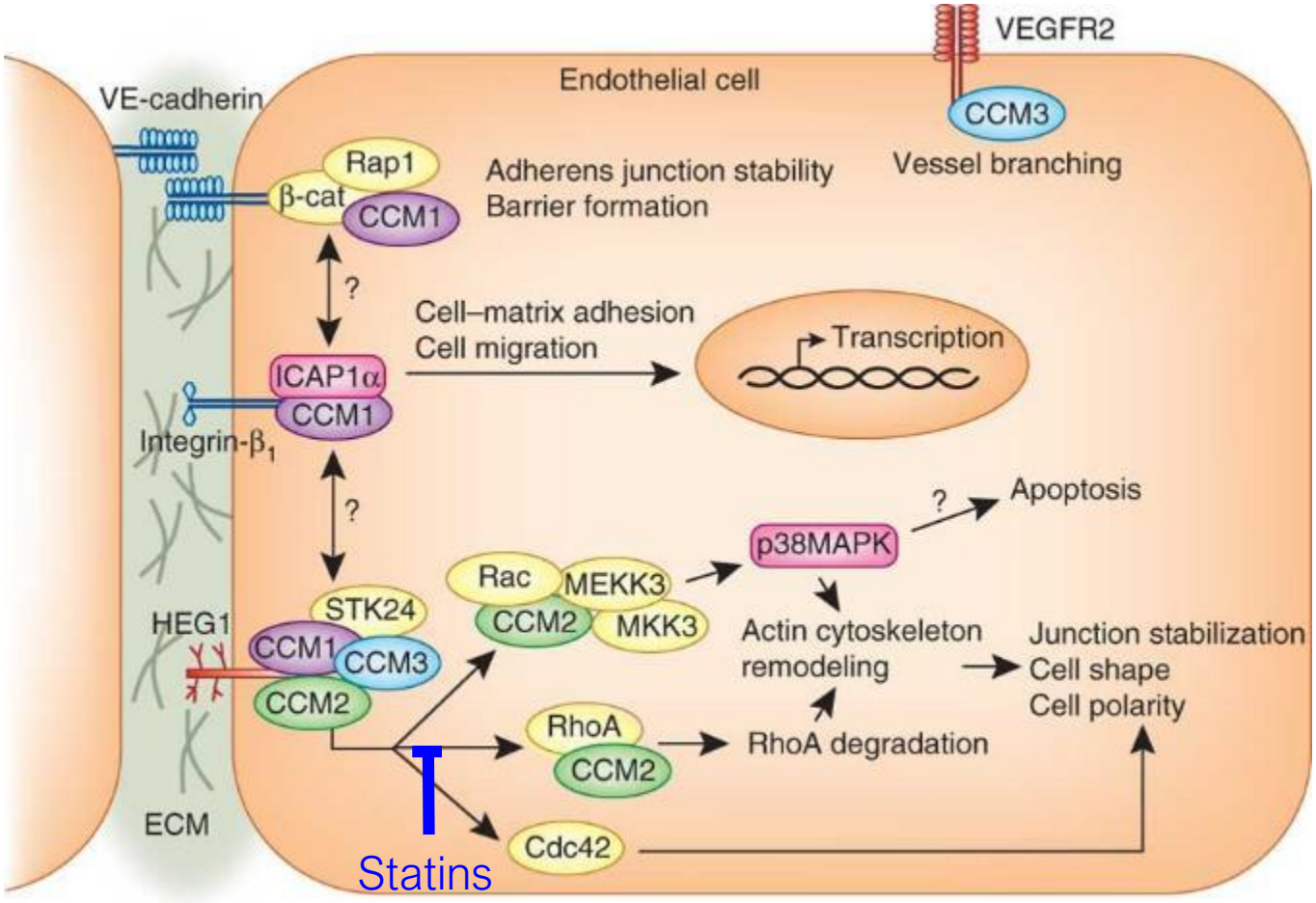
pharmaceuticals

CEREBRAL CAVERNOUS MALFORMATION



THE STORY OF ONE RARE GENETIC DISEASE

The Reductionist Approach



Storkebaum, et al. Nature Neuroscience, 2011

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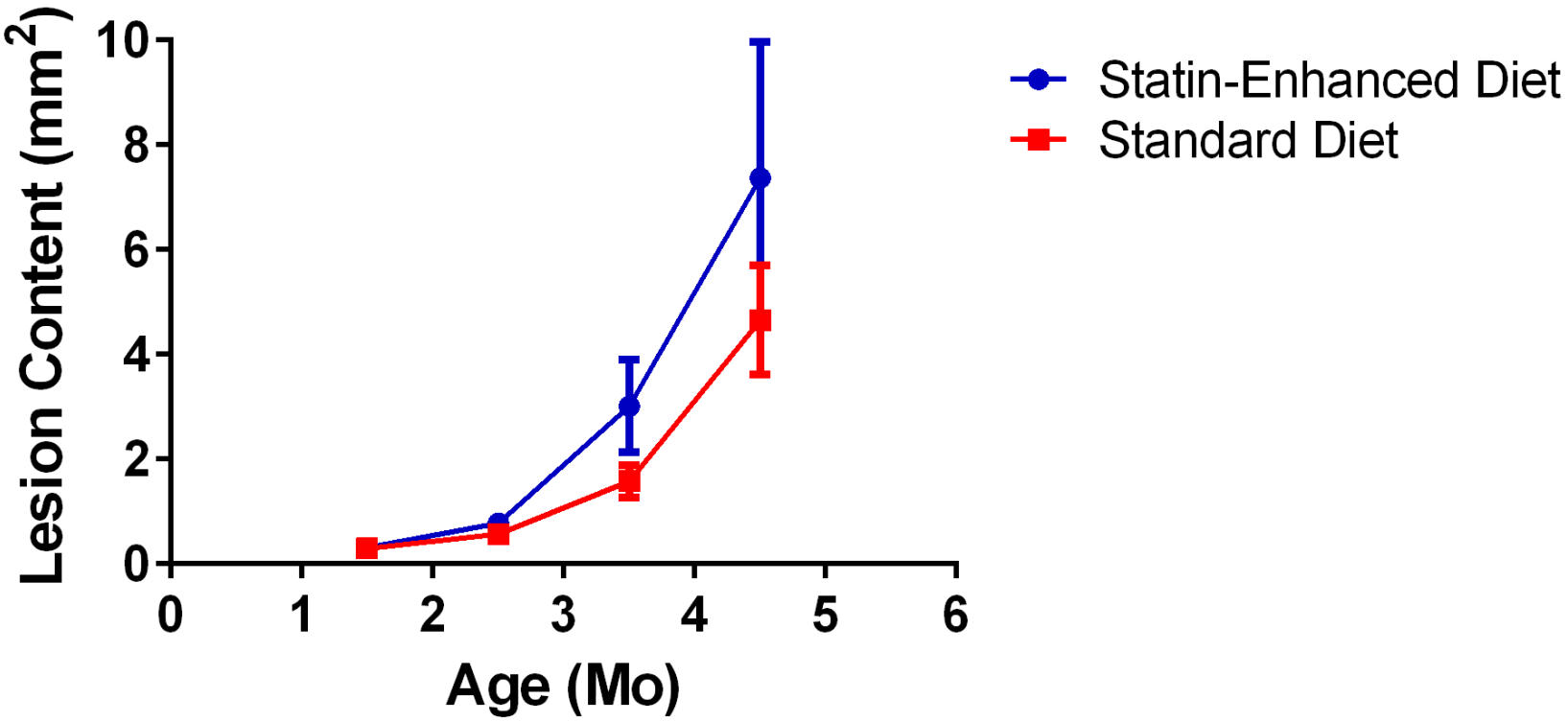
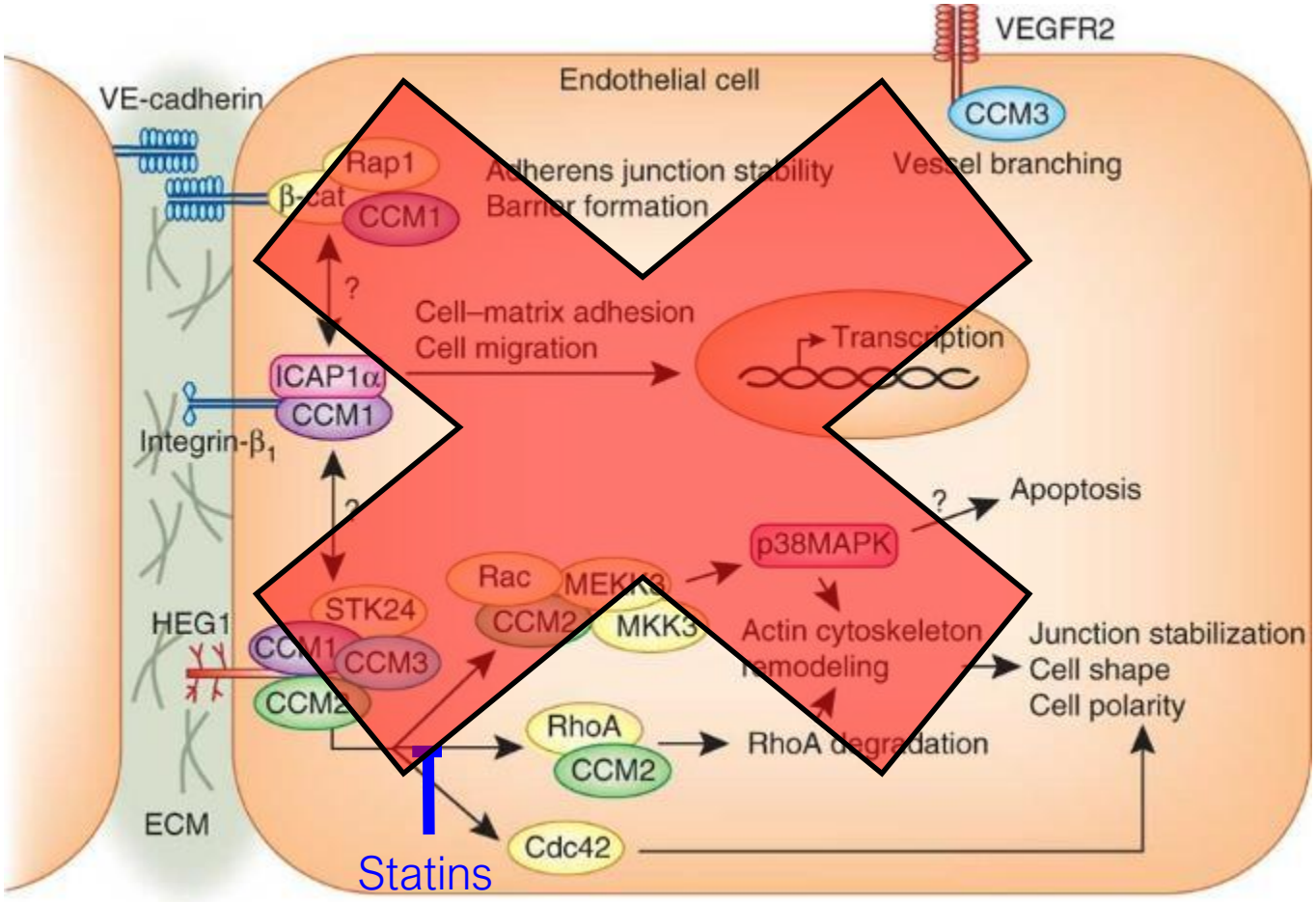
Rational Target-Based Discovery for Complex Rare Disease?



Gibson, et al., Circulation. 2015

The Reductionist Approach



Storkebaum, et al. Nature Neuroscience, 2011

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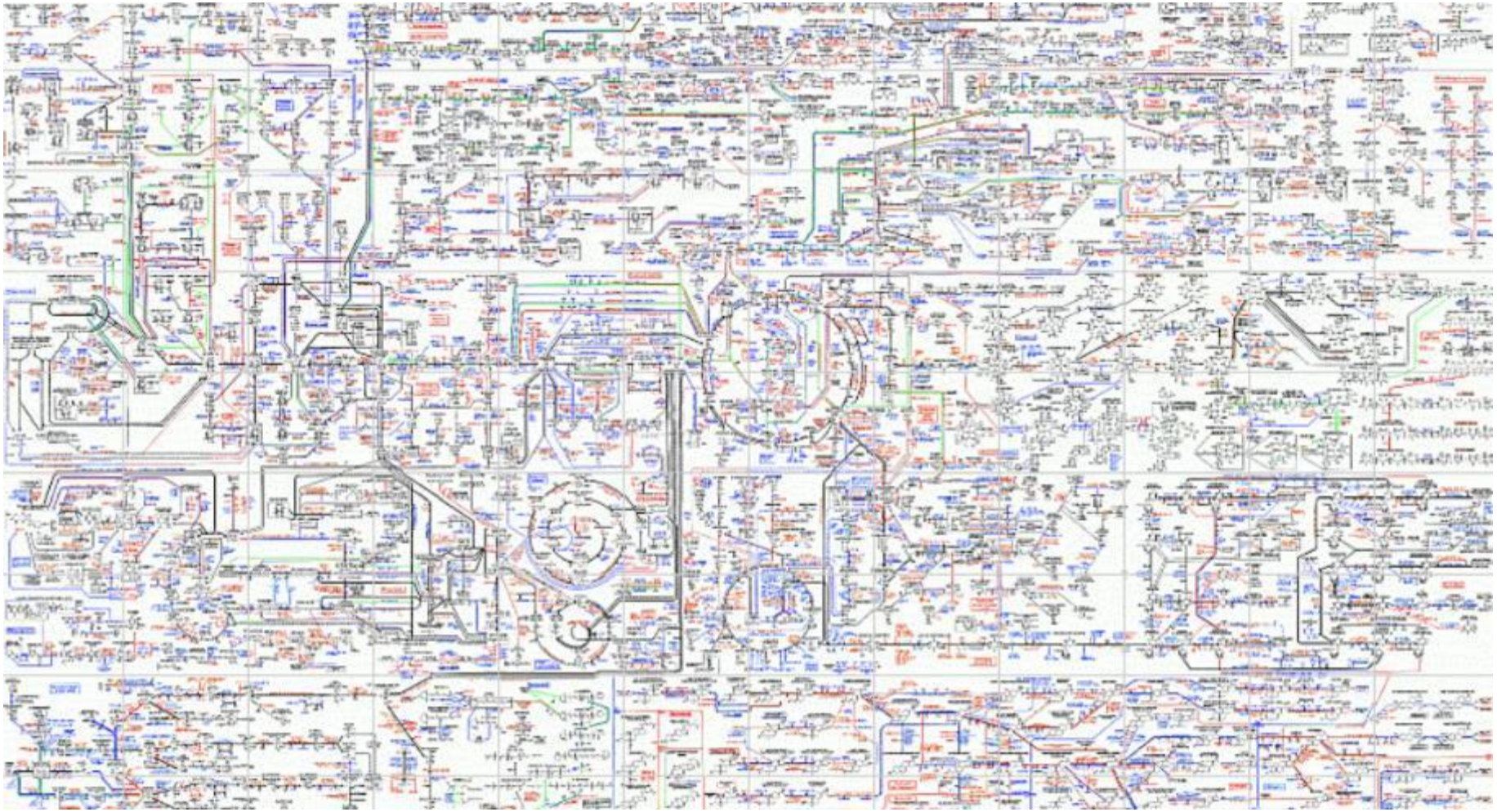
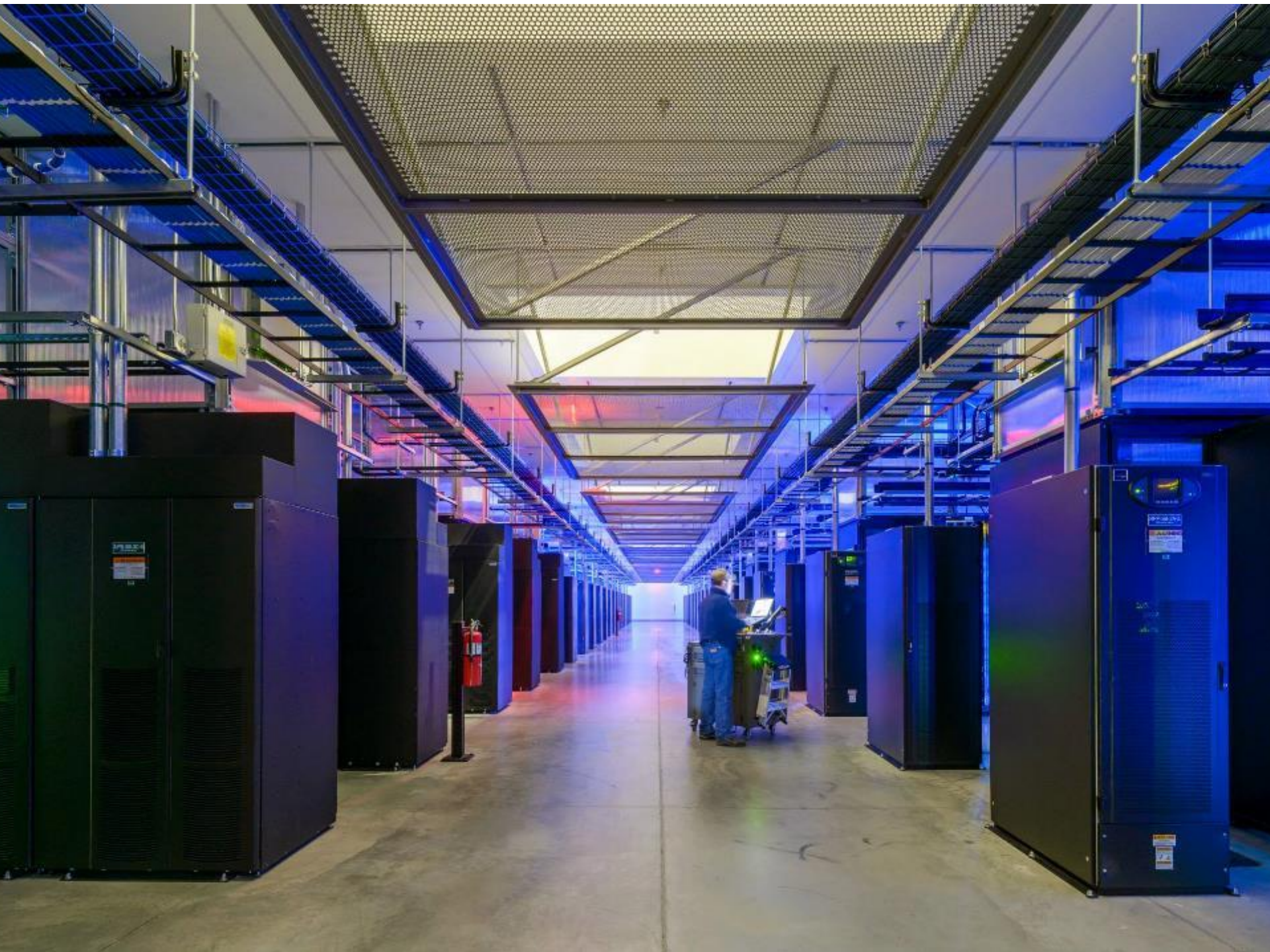
The Problem with Biology



RECURSION


telecom
20.0°
20.0°




sky
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tree
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STOP
car
car
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car
car
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road
road
road
road
road
road
building
grass

A woman is throwing a **frisbee** in a park.

A **dog** is standing on a hardwood floor.

A little **girl** sitting on a bed with a teddy bear.

A group of **people** sitting on a boat in the water.

Massive advances in leveraging AI to understand complex networks

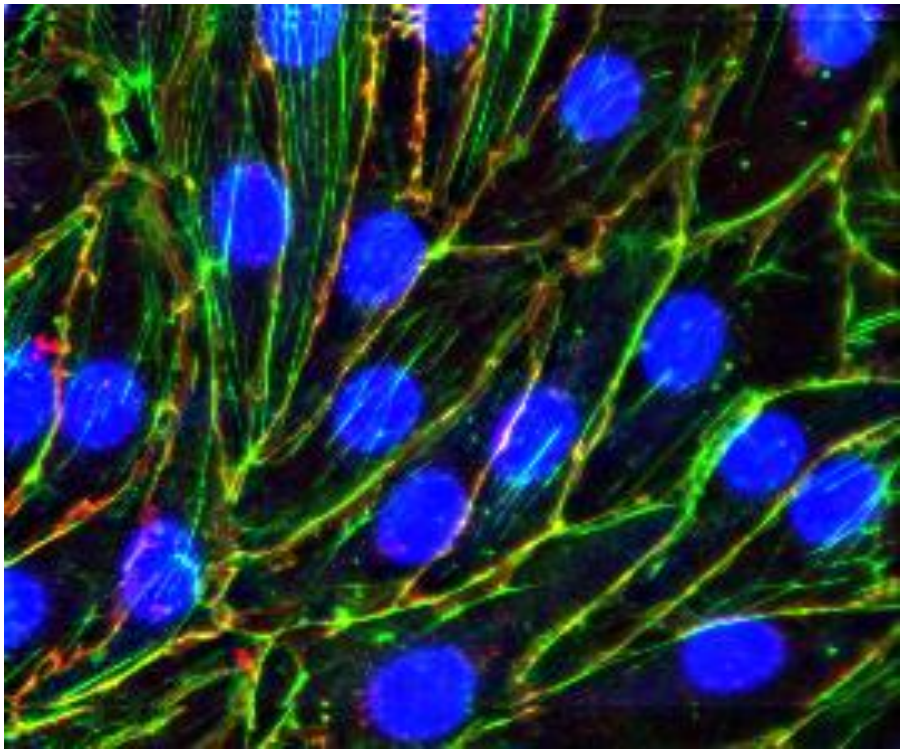
Massive advances in leveraging AI to recognize patterns in images

NEED millions or billions of data points to train these systems well

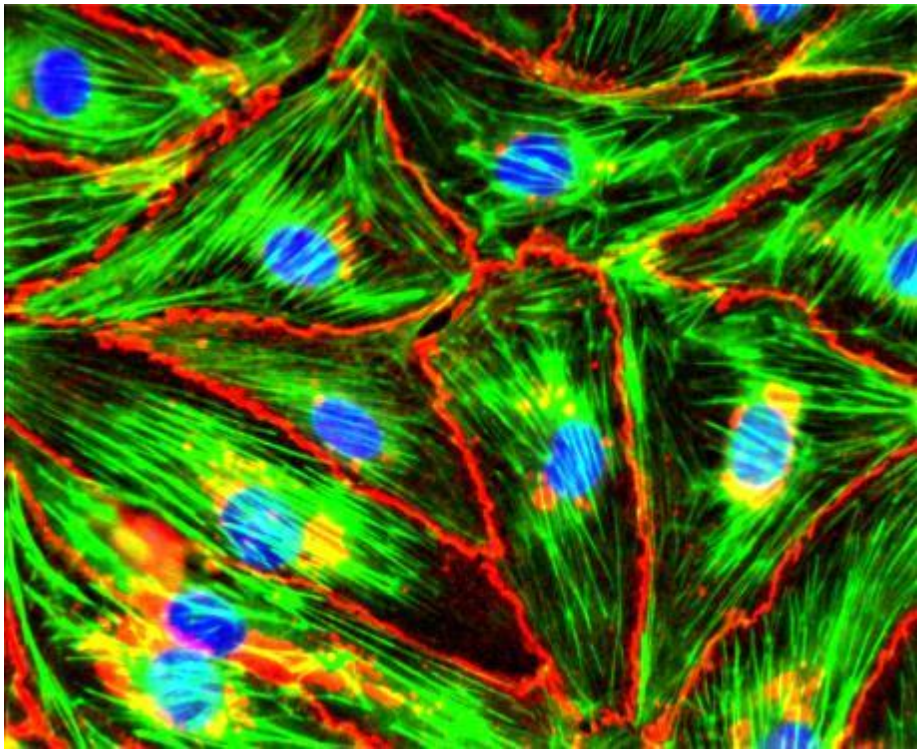
<u>Can we turn biology into a data science problem?</u>

RECURSION

Target-Agnostic, Unbiased, High-Content Phenotypic Screening



siCTRL



siCCM2

VE Cadherin Actin DNA

Gibson, et al., Circulation. *2015*

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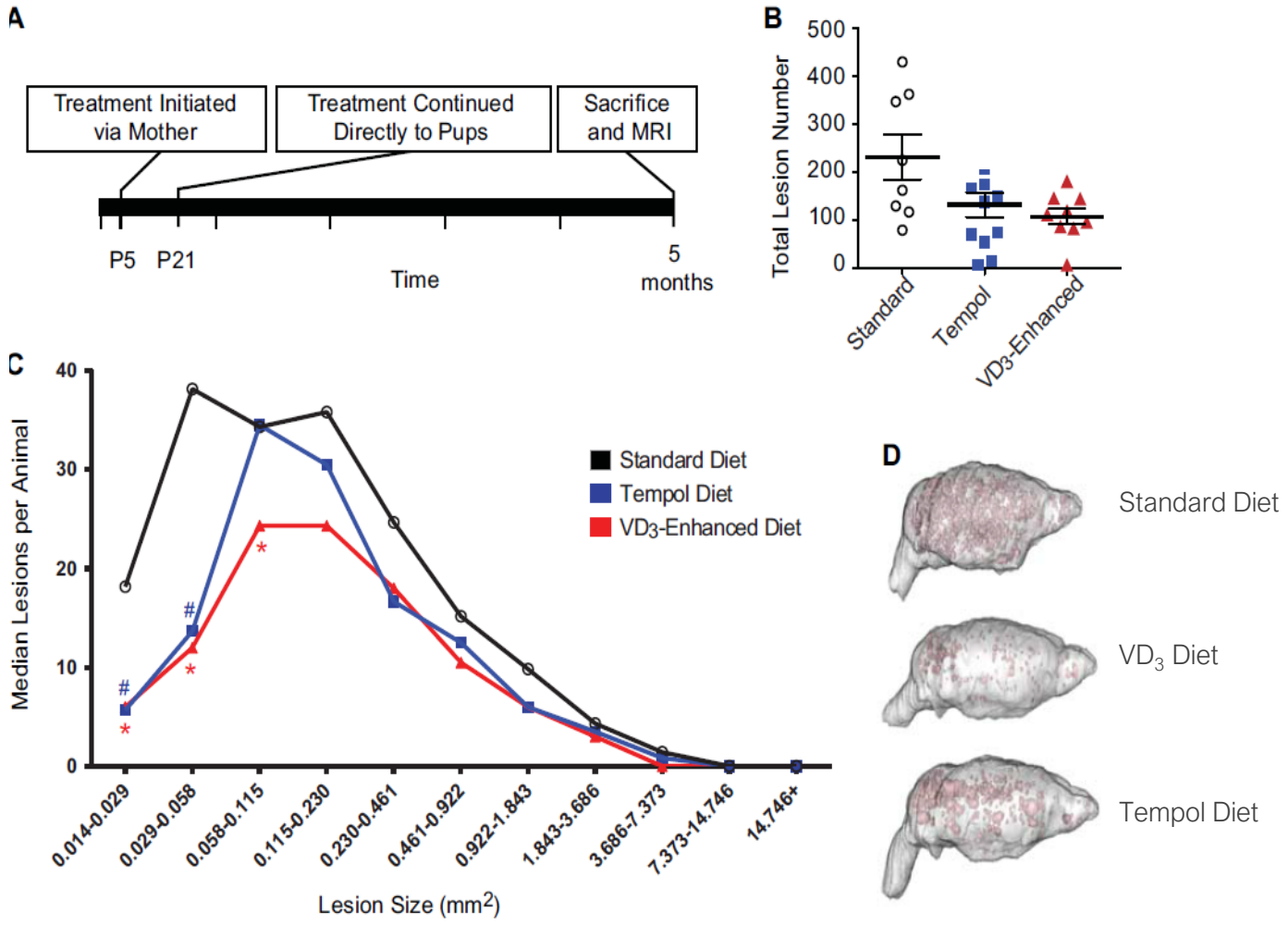
Two treatments identified using ML rescue lesion number in CCM mice



Gibson, et al., Circulation. *2015*

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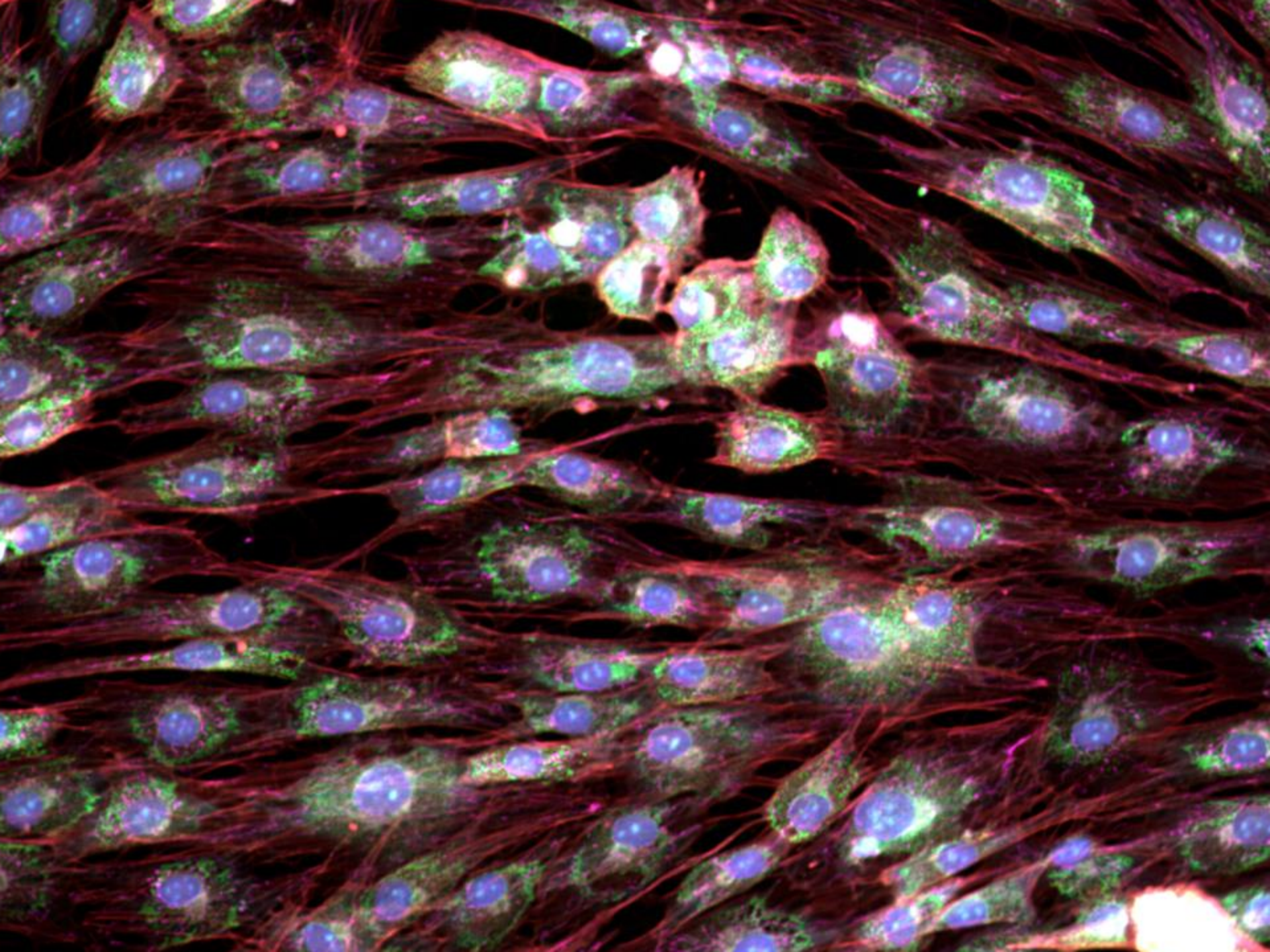
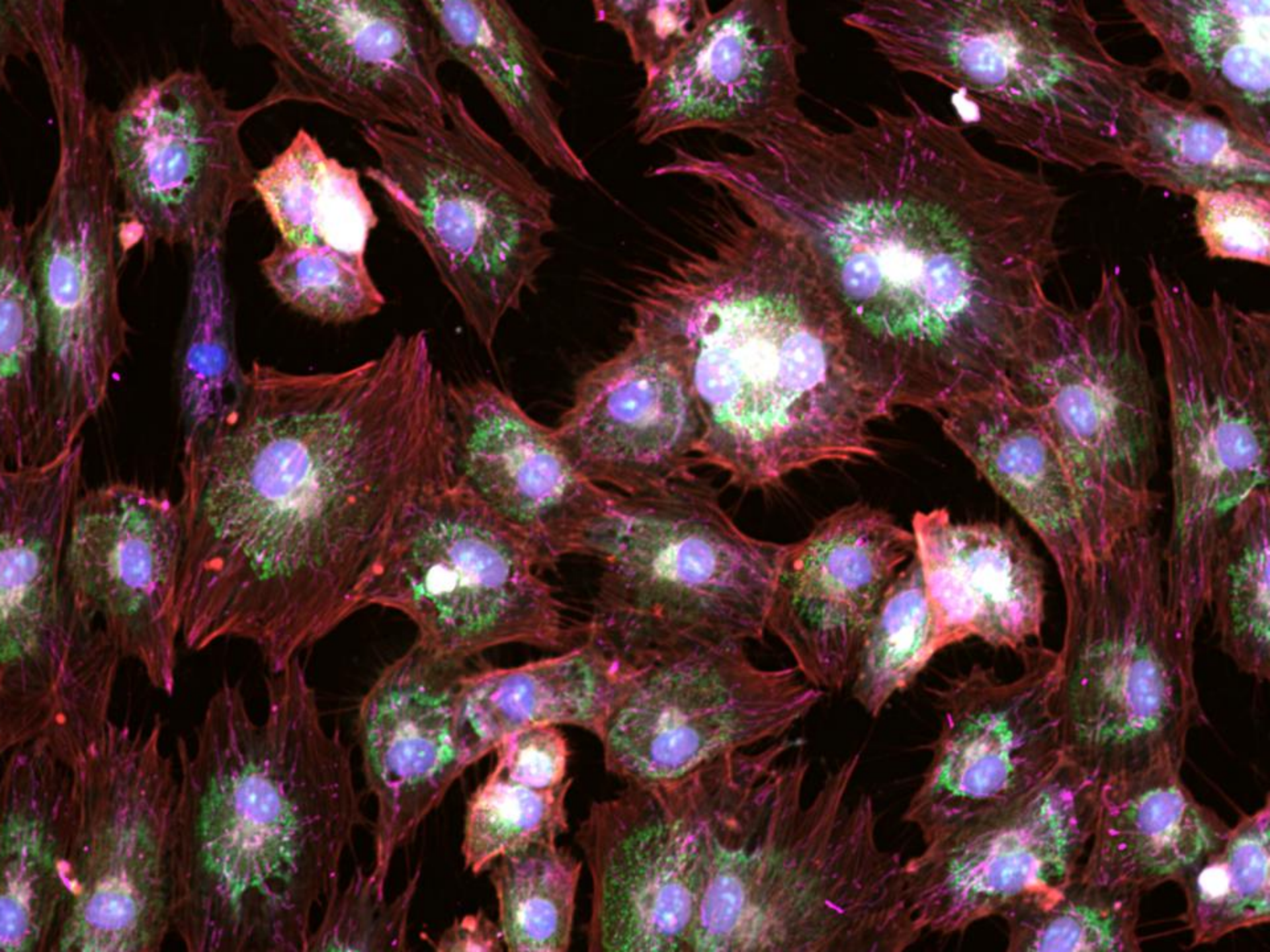
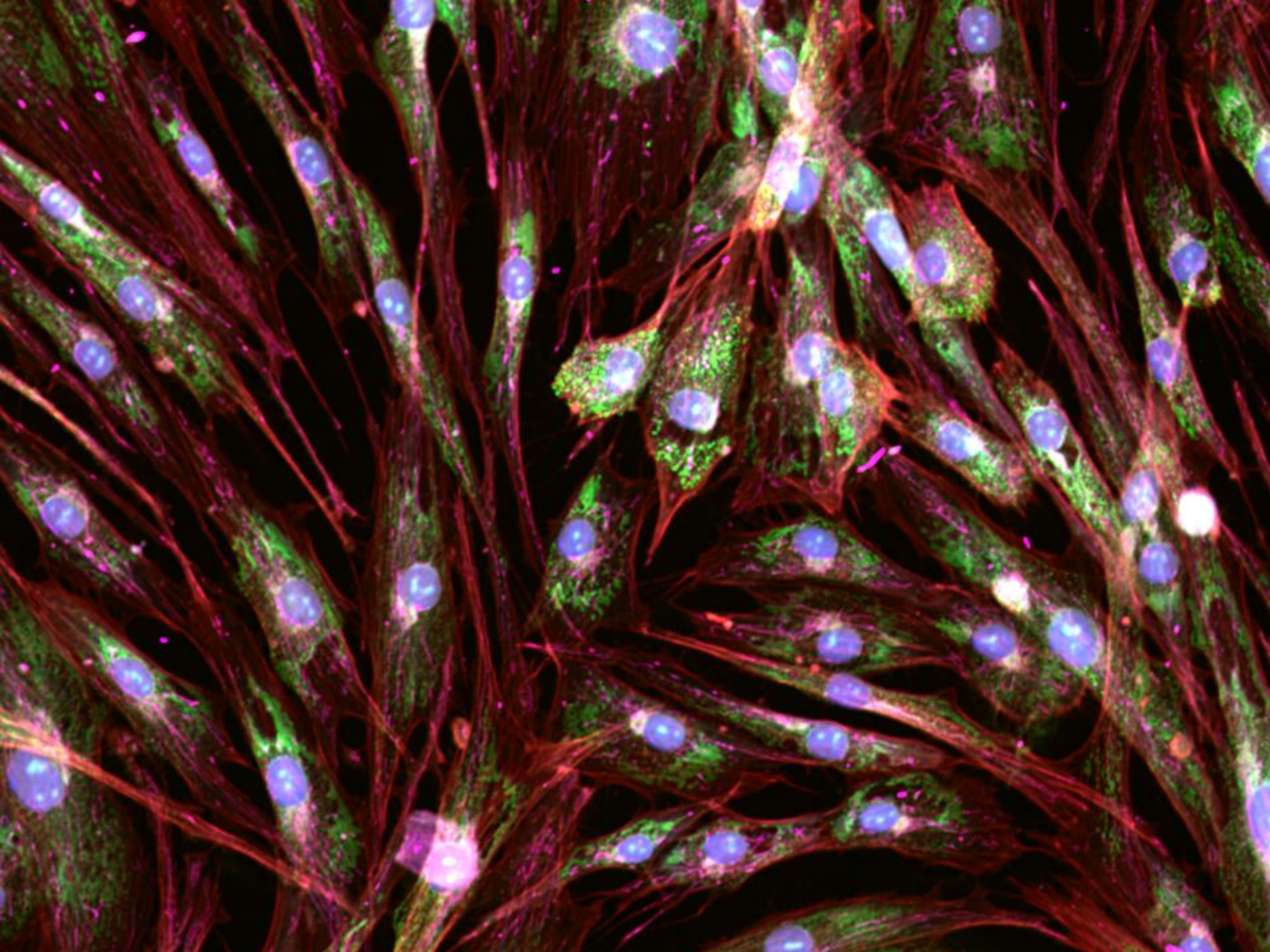
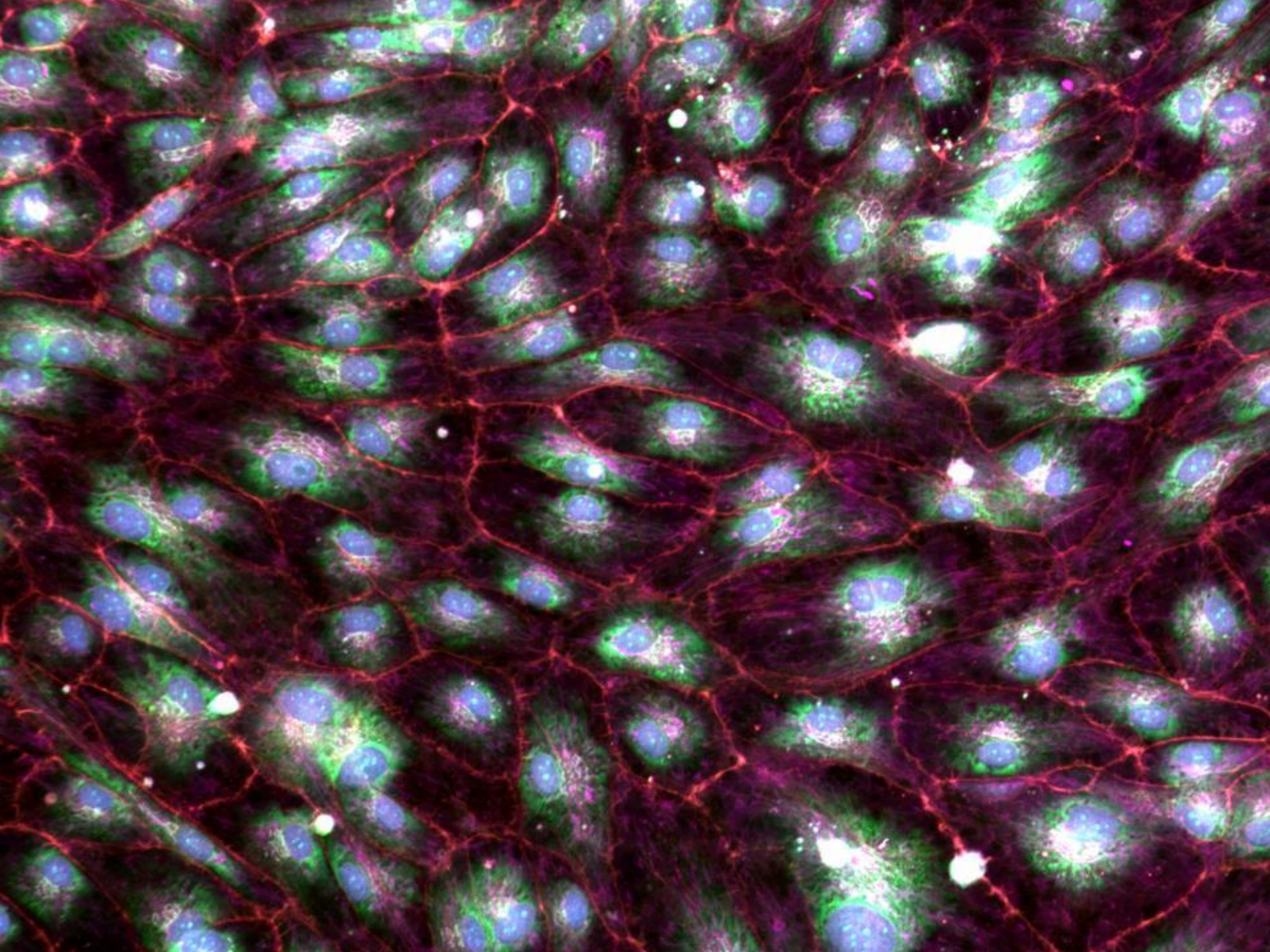


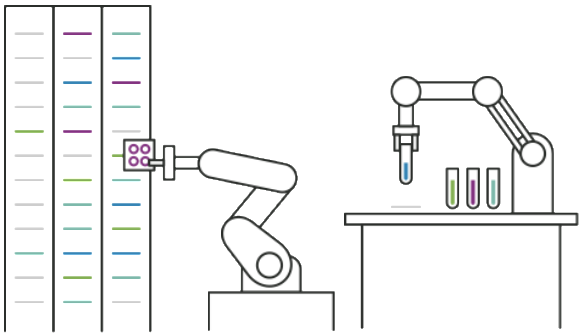






‘DEEP TECH’ APPROACH TO DISCOVERY

PROPRIETARY DATA FUELS SOPHISTICATED MACHINE LEARNING



Automated Biology

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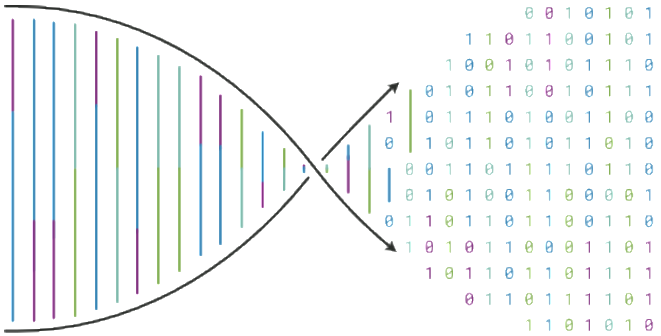
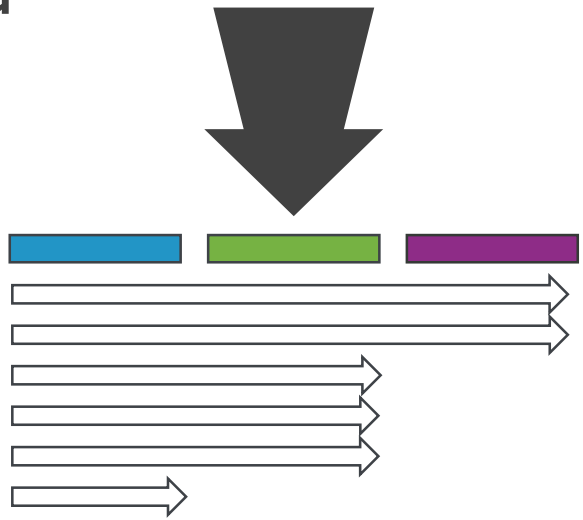


Artificial Intelligence



Massively Parallel Drug Discovery

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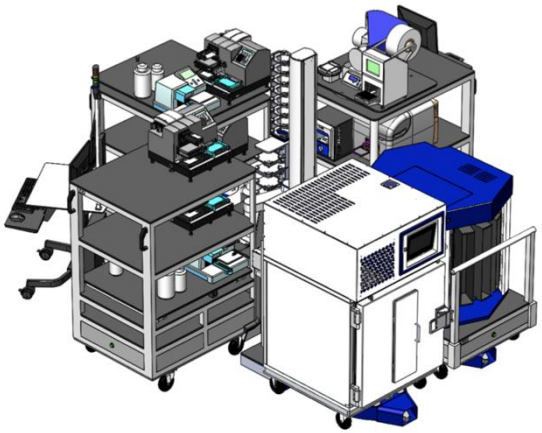
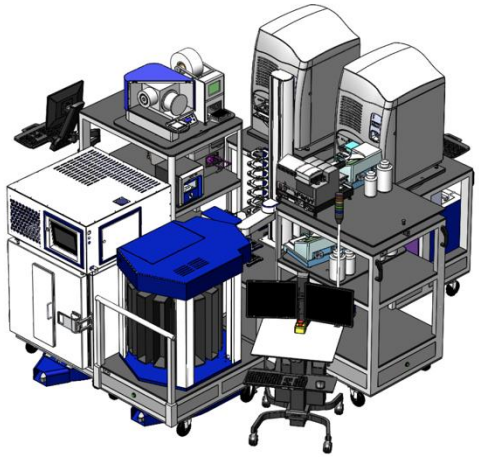
STATE-OF-THE-ART AUTOMATION

PRECISION-FLEX WORK CELLS

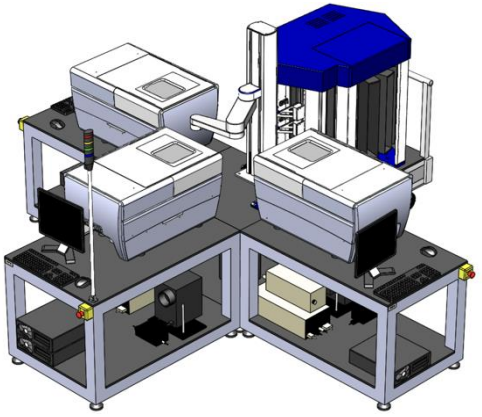
300
384-plates
each week



>100
diseases
per year



>90k
Perturbations
each week



Powered by: HighRes biosolutions

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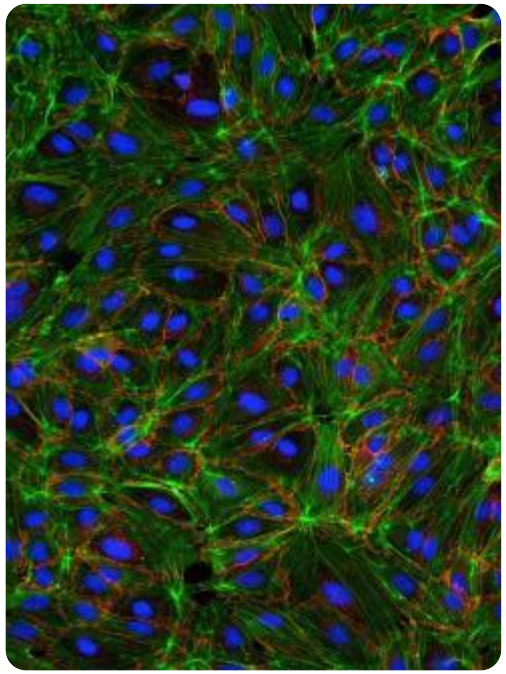
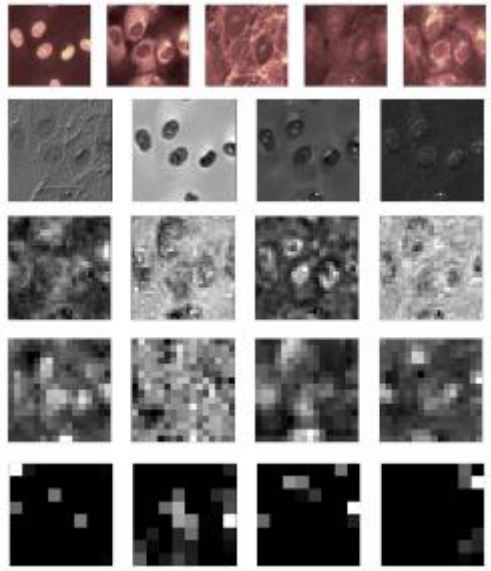
In Biology Structure Suits Function

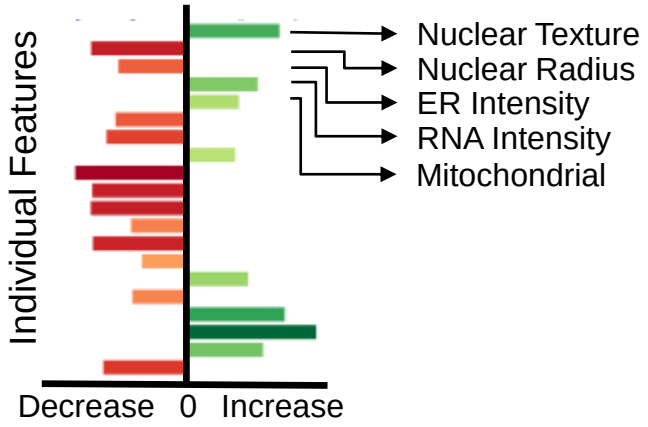
2 Million
images
each week



Deep Learning &
Feature Extraction



Disease
Phenotypic Fingerprints



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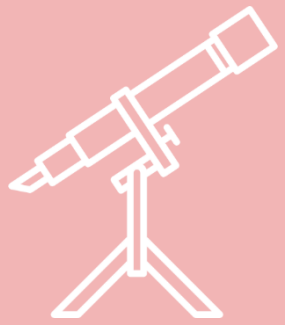
THE VISION

SHORT TERM

RARE GENETIC DISEASE

100+ genetic disease treatments by 2025



INTERMEDIATE TERM

EXPAND FOCUS

Disrupt drug discovery across new disease areas (aging, oncology, infectious disease) , and new applications (diagnostics, new chemical entity discovery)

VISION

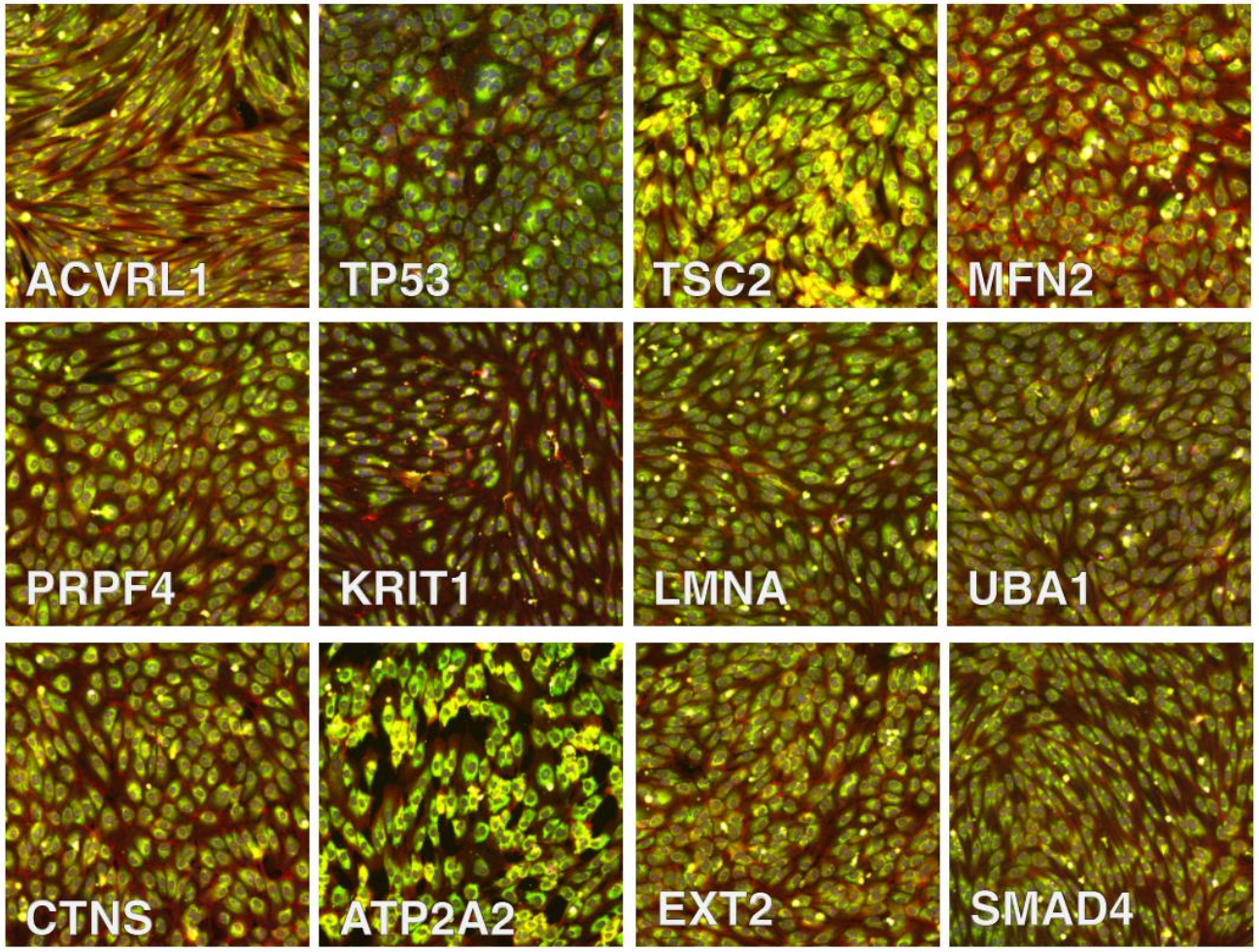
SYSTEMS BIOLOGY

Leverage technology to map most of human biology
-
Impact and monetization potential extreme

RECURSION

Rare-Disease Drug Discovery

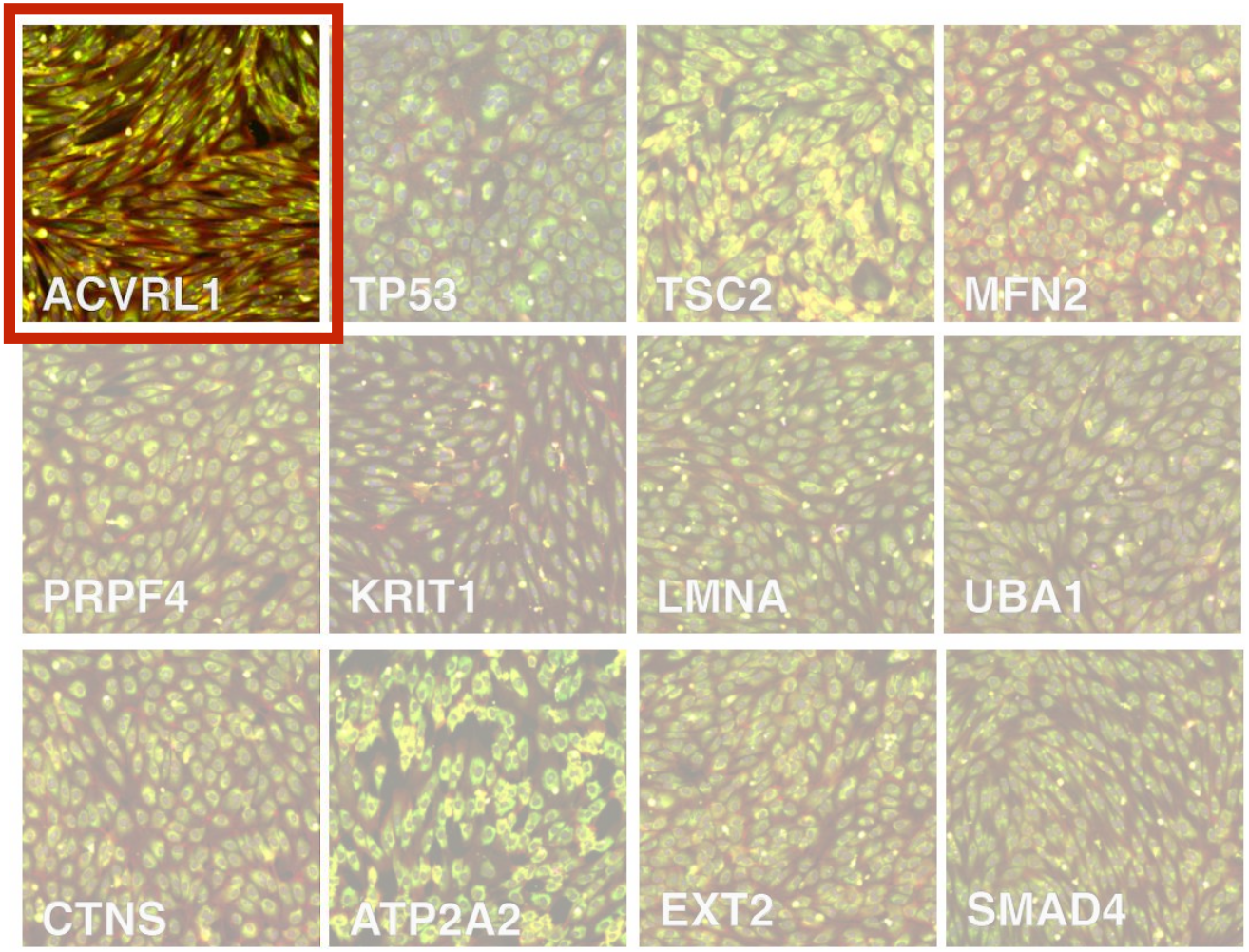
Genetic loss-of-function produces robust phenotypes



RECURSION

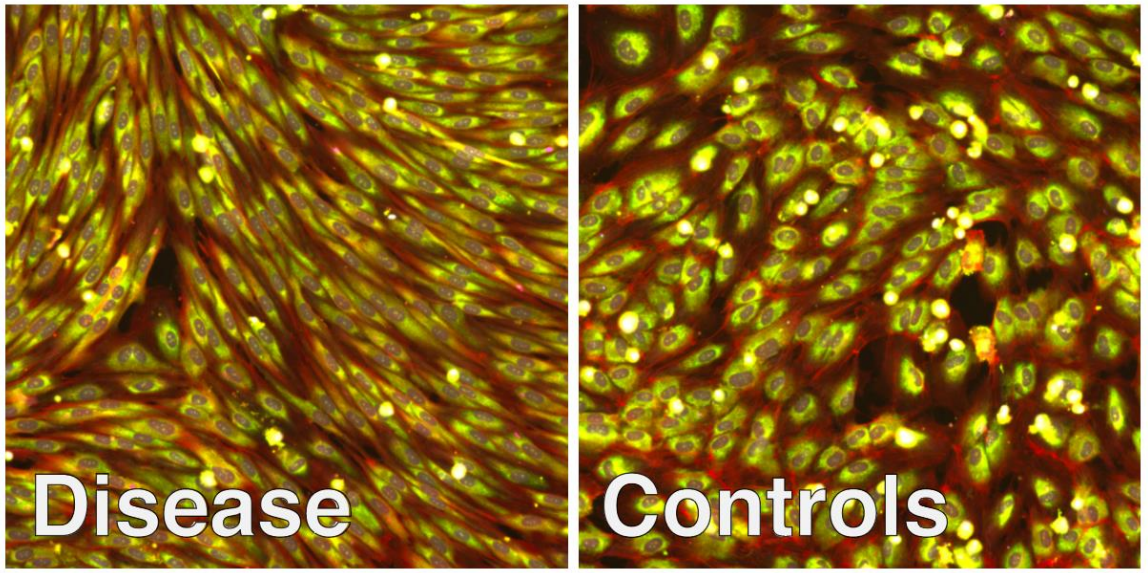
Hereditary Hemorrhagic Telangiectasia (HHT)

Genetic loss-of-function produces robust phenotypes

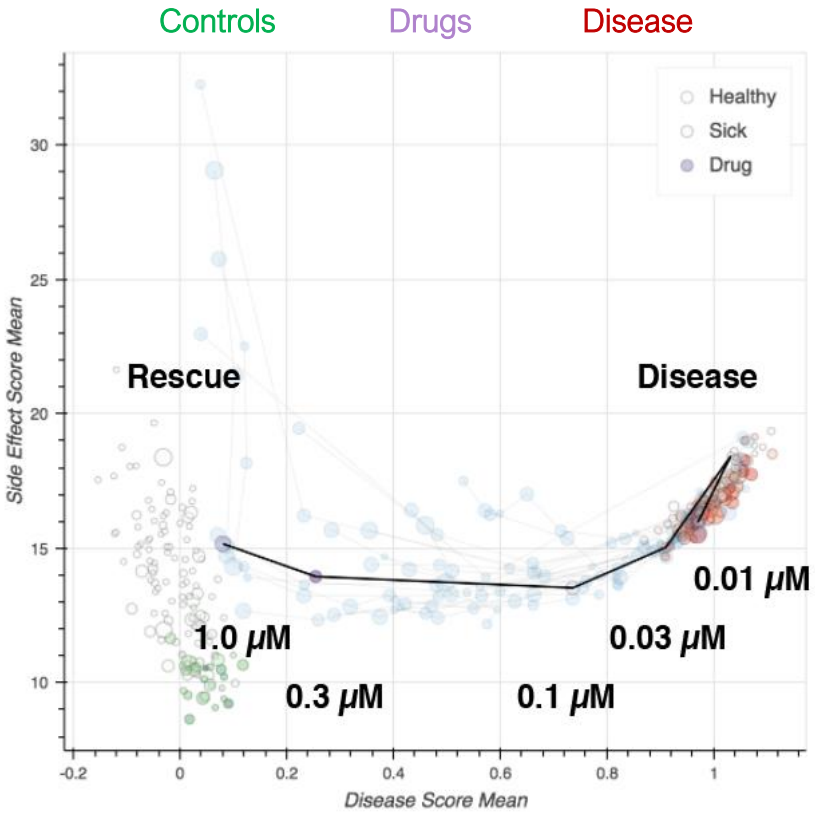


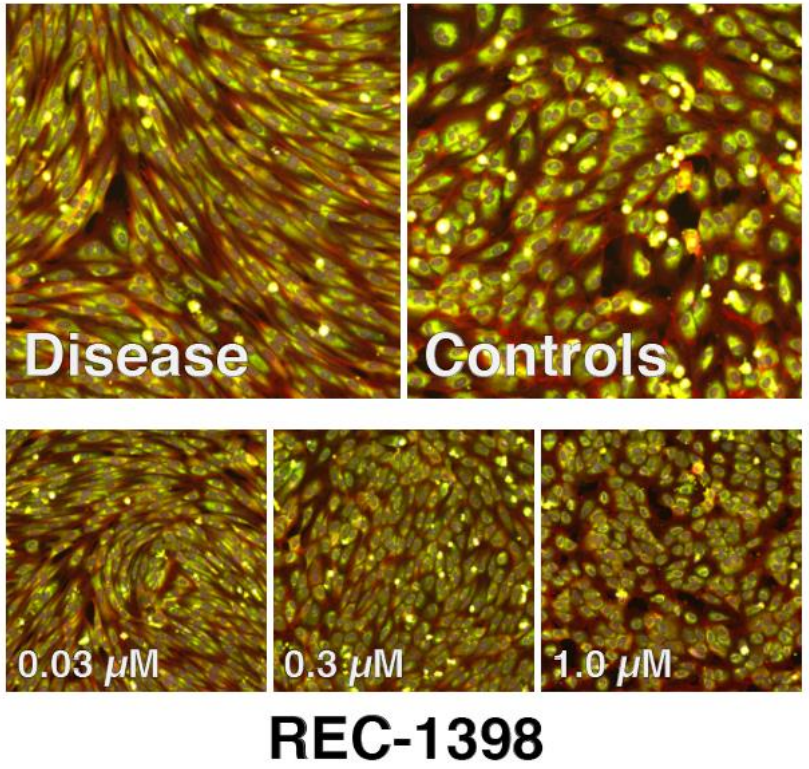
RECURSION

HHT Cellular Morphology



Rescue of Morphological Features



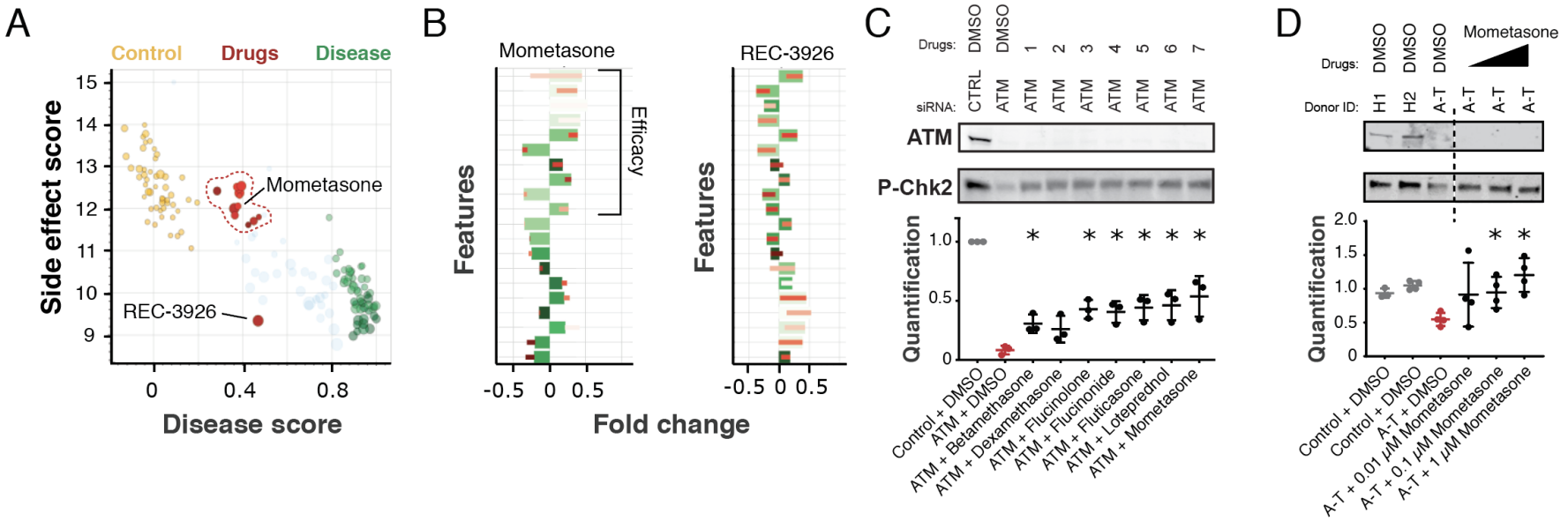


RECURSION

FINDING NEW TREATMENTS
VALIDATED BIOLOGY

We & our Discovery Partners act on validated innovations.

With broad biological expertise in-house, insights are always validated in gold-standard assays in vitro and may also be validated in vivo in certain circumstances. Here we show a subset of disease specific assays for Ataxia Telangiectasia. Drugs identified rescue in our screen rescue levels of Chk2 phosphorylation.



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PLATFORM VALIDATION

Recursion has 're-discovered' multiple drugs and target classes that are already in or beyond Phase 2, validating our platform.

Disease	Target Class	Drug (Sponsor)	Phase	Clinical trial
Ataxia Telangiectasia	Glucocorticoid	Betamethasone	Phase 2	Leuzzi et. Al 2015
	Glucocorticoid	Dexamethasone	Phase 2	Zannolli et. Al 2012
Spinal muscular atrophy	HDAC	Valproic acid	Phase 1/2/3	NCT00661453; NCT00227266; NCT01671384
Neurofibromatosis type 2	mTOR	Everolimus (Novartis) AZD2014 (Astra Zeneca)	Phase 2 Phase 2	NCT01419639 NCT02831257
	VEGF c-KIT	Axitinib PTC299 (PTC Pharma) Sunitinib (Pfizer)	Phase 2 Phase 2 Phase 2	NCT02129647 NCT00911248 NCT00589784
	ERBB2/ EGFR	Lapatinib (GSK)	Phase 2	NCT00973739
Metastatic Bladder Cancer with TSC1/2 Mutations	mTOR	Sapanisertib (Takeda)	Phase 2	NCT03047213

In many cases, we have identified potentially more efficacious targets from each of these classes.

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GENETIC DISEASE
HUNDREDS OF UNIQUE MODELS

SUBSET OF CURRENT GENETIC DISEASE
MODELS

Gene	Disease
ANG	Amyotrophic lateral sclerosis
APC	Adenomatous polyposis coli
ARSA	Metachromatic leukodystrophy
ATM	Ataxia telangiectasia
ATP2A2	Darier disease
ATP8B1	Chelestasis
CACNA2D4	Retinal cone dystrophy
CDKN2A	Melanoma astrocytoma syndrome
CCM2	Cerebral Cavernous Malformation
CHD2	CHD2 myoclonic encephalopathy
CHMP2B	Frontotemporal dementia
CLN8	Ceroid lipofuscinosis
DGKE	Nephrotic syndrome
EXT1	Hereditary multiple exostoses
FANCE	Fanconi anemia
HEXB	Sandhoff disease
ISPD	Walker-Warburg congenital muscular dystrophy
KANSL1	Parkinson disease
KMT2D	Kabuki make-up syndrome
KRT9	Epidermolytic palmoplantar keratoderma
KRIT1	Cerebral cavernous malformation
LAMA4	Dilated cardiomyopathy
LEMD3	Dermatofibrosis lenticularis disseminata
LMF1	Lipase deficiency
LRBA	Common variable immunodeficiency
MAGEL2	Prader-willi-like syndrome

Gene	Disease
MCOLN1	Mucolipidosis type IV
MFN2	Charcot-Marie-Tooth (Axonal)
MSH2	Torre-Muir syndrome
NBEAL2	Gray platelet syndrome
NF2	Neurofibromatosis Type II
NOD2	Crohn disease
NPHP1	Nephronophthisis, juvenile
NSD2	Wolf-Hirschhorn syndrome
PAFAH1B1	Classical lissencephaly
PLEC	Epidermolysis bullosa simplex
PNPLA2	Neutral lipid storage disease with myopathy
PRPF31	Retinitis pigmentosa
PRRT2	Paroxysmal kinesigenic choreoathetosis
PSAP	Combined SAP, Atypical Gaucher, Krabbe Disease
RAI1	Smith-Magenis syndrome
SDHC	Paraganglioma and gastric stromal sarcoma
SMAD4	Hereditary Hemorrhagic Telangiectasia
SMARCB1	Coffin-Siris Syndrome
SMN1	Spinal Muscular Atrophy
SLC17A5	Sialic acid storage disease
TARDBP	Amyotrophic lateral sclerosis
TNPO3	Limb-girdle muscular dystrophy
TP53	Li-Fraumeni syndrome / Cancers (various)
TSC2	Lyphangioleiomyomatosis
UBA1	Spinal Muscular Atrophy
VWF	Von Willebrand disease type 1

Updated August 2017

RECURSION

Recursion Asset Pipeline

IN VITRO

- TUBEROUS SCLEROSIS COMPLEX (TSC1)
- CHARCOT-MARIE-TOOTH (MFN2)
- HEREDITARY HEMORRHAGIC TELANGIECTASIA (ACVRL1)
- RETINITIS PIGMENTOSA (MULTIPLE)
- RUBINSTEIN-TAYBI SYNDROME (CREBBP)
- CYSTINOSIS (CTNS)
- EMERY-DREIFUSS MUSCULAR DYSTROPHY/PROGERIA (LMNA)
- HEREDITARY HEMORRHAGIC TELANGIECTASIA (ACVRL1)
- NEUROFIBROMATOSIS TYPE 2 (NF2)
- PEUTZ-JEGHERS SYNDROME (STK11)
- USP7- ULTRA-RARE DISEASE
- LIMB-GIRDLE MUSCULAR DYSTROPHY (POMT1)
- COFFIN-LOWRY SYNDROME (RPS6KA3)
- DARIER DISEASE (ATP2A2)
- HEREDITARY MULTIPLE OSTEOCHONDROMAS (EXT1, EXT2)
- CEREBRAL CAVERNOUS MALFORMATION (KRIT1)
- JP / HEREDITARY HEMORRHAGIC TELANGIECTASIA (SMAD4)
- UNDISCLOSED PARTNER INDICATION PARTNER 1, PROGRAM 1
- UNDISCLOSED PARTNER INDICATION PARTNER 1, PROGRAM 2
- UNDISCLOSED PARTNER INDICATION PARTNER 1, PROGRAM 3
- UNDISCLOSED PARTNER INDICATION PARTNER 1, PROGRAM 4
- UNDISCLOSED PARTNER INDICATION PARTNER 1, PROGRAM 5
- UNDISCLOSED PARTNER INDICATION PARTNER 2, PROGRAM 1

IN VIVO

- SPINAL MUSCULAR ATROPHY (SMN) PROGRAM 1
- SPINAL MUSCULAR ATROPHY (SMN) PROGRAM 2
- DIAMOND BLACKFAN ANEMIA (RPS19)
- METACHROMIC LEUKODYSTROPHY/ATYPICAL GAUCHER DISEASE (PSAP)

PRE-IND

- CEREBRAL CAVERNOUS MALFORMATION PROGRAM 1 *(IND expected Q1, 2018)*
- ATAXIA-TELANGIECTASIA PROGRAM 1 *(IND expected Q1, 2018)*
- ATAXIA-TELANGIECTASIA PROGRAM 2

30+

Discovery Programs

RECURSION pharmaceuticals

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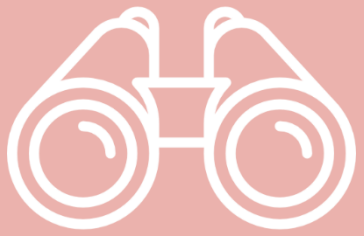
THE VISION



SHORT TERM

RARE GENETIC DISEASE

100+ genetic disease treatments by 2025

INTERMEDIATE TERM

EXPAND FOCUS

Disrupt drug discovery across new disease areas (aging, oncology, infectious disease) , and new applications (diagnostics, new chemical entity discovery)

VISION

SYSTEMS BIOLOGY

Leverage technology to map most of human biology

-

Impact and monetization potential extreme

RECURSION

DISEASE MODELS
IMMUNOLOGY & INFLAMMATION

Recursion is interrogating more than **150 immunology disease models** spanning inflammation, auto-immune, oncology, and developmental pathologies.

Mediator	Condition	Mediator	Condition
TNFα	Rheumatoid Arthritis, Crohns Disease, Ulcerative Colitis	IL-5	Dermatitis Herpetiformis
IL-1α	Dermatomyositis	IL-8	Inflammatory Bowel Disease
IL-1β	Pemphigus	TGFβ	Metastasis, Chemoresistance, Fibrosis
IL-1 family	Type I Diabetes	MCPs	Multiple Sclerosis, Ulcerative Colitis
IL-1R	Experimental Autoimmune Encephalitis (EAE)	RANTES	Crohn's Disease, EAE
TRAIL	Autoimmune Arthritis	GM-CSF	Tumor Invasion, Immune development
RANKL	Autoimmune Arthritis	Eotaxin	Allergic Inflammation, Allergic Colitis
TALL-1	Lupus and Lupus-Like Syndromes	IL-17	Asthma, Psoriasis, Transplant Rejection, Multiple Sclerosis
IL-2	Haemolytic Anemia, Ulcerative Bowel Diseases	IL-18	Allergic Inflammation, Rheumatoid Arthritis
IFNγ	Virus-induced Diabetes, EAE, RR-MS	IL-13	Asthma
IFNα	Diabetes	IL-23	Tumor Vascularization, Autoimmune Arthritis
IL-6	Colonic and Pancreatic inflammation, Systemic Sclerosis	IL-10	Colitis, Tumorigenesis, Immune-tolerance
IL-12	Ulcerative Colitis, Rheumatoid Arthritis	IL-4	Lupus, Rheumatoid Arthritis, Colitis
IL-15	Autoimmune Arthritis, Crohn's Disease, T-cell Leukemia	IL-33	Asthma, Anaphylaxis, Dermatitis

Recursion is able to perform an unbiased screen for both agonists and antagonists of these pathways

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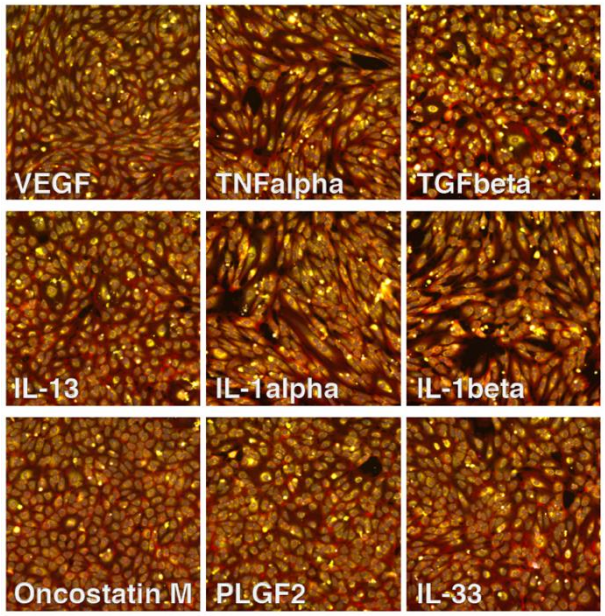
PHENOMICS ENABLED IMMUNOLOGY

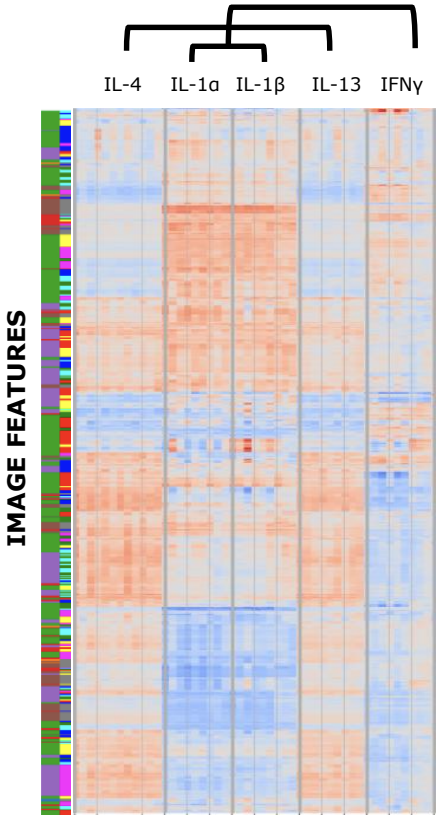
CYTOKINES, CHEMOKINES, AND SOLUBLE FACTORS

Soluble factor perturbations yield highly sensitive, meaningful, and complex phenotypes that can be leveraged to accelerate small molecule drug discovery for traditionally refractory pleiotropic disease pathways.

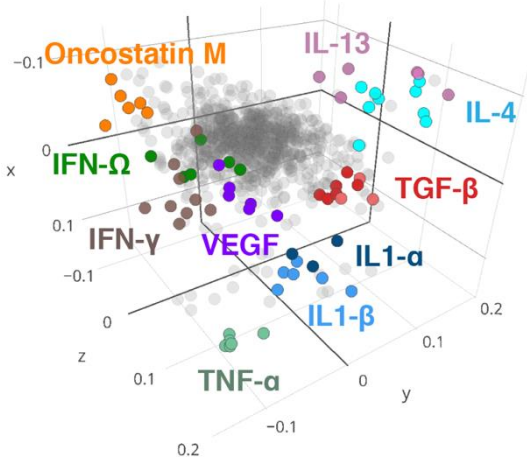
INFORMATIVE IMAGING



HIGH-DIMENSIONAL QUANTIFICATION



MEANINGFUL CLUSTERING



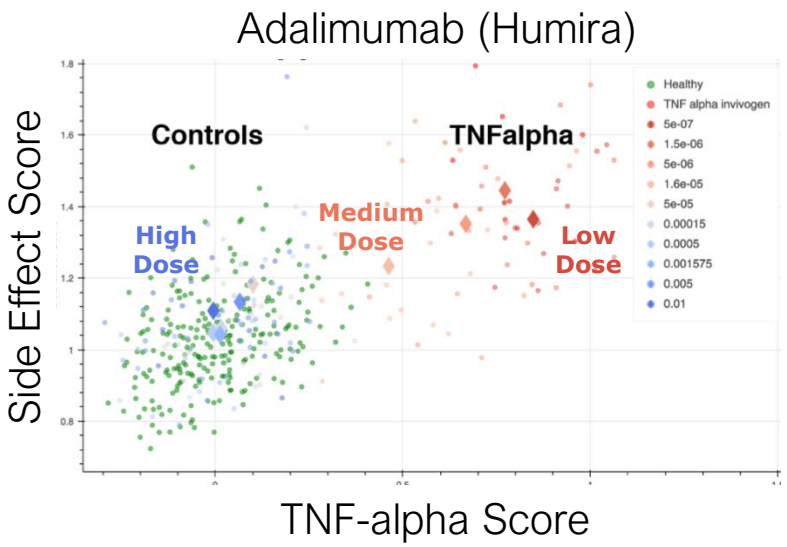
RECURSION

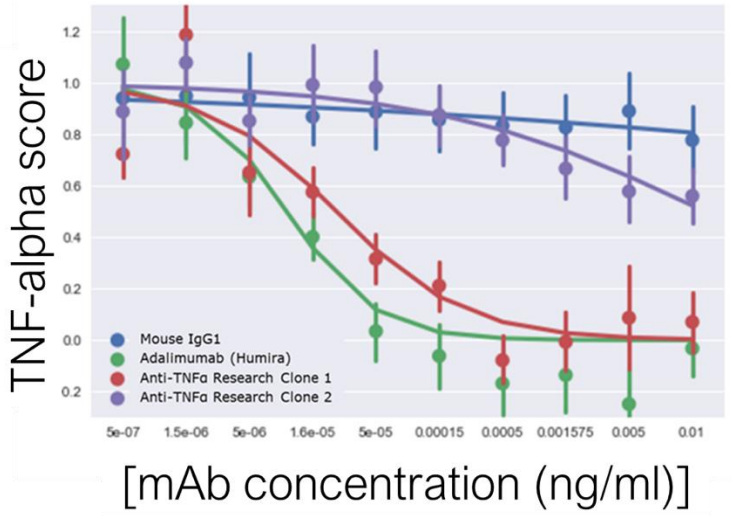
IMMUNOLOGY DRUG DISCOVERY

PHENOTYPIC ASSAYS FOR HIT ID OR BIOSIMILAR OPTIMIZATION

Highly sensitive rescue of TNF-alpha structural phenotype can be leveraged for hit or target identification. In a cellular context, Humira® demonstrates a superior efficacy profile compared to research antibody clones.

CELLULAR ASSAYS WITH BIOCHEMICAL SCALE SENSITIVITY





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PHENOMICS ENABLED IMMUNO-ONCOLOGY

MODULATING MACROPHAGE POLARITY

Classically (M1) and alternatively activated macrophages (M2a, M2c, M-CSF induced "TAMs") present with distinct and meaningful high-dimensional cellular phenotypes, allowing for robust interrogation of macrophage modulators.

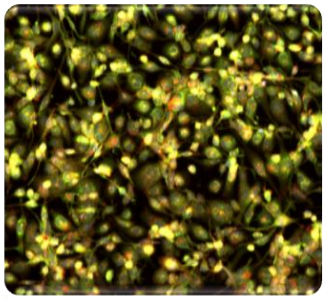
INTEGRATED CELLULAR PHENOTYPES

MOLECULAR PHENOTYPING

	M1	M2a
Marker expression	CD68 CD86 CD80 MHC II IL-1R TLR2 TLR4 iNOS SOCS3	CD163 MHC II SR MMR/CD206 CD200R TGM2 DecoyR IL-1R II *Mouse only:* *Ym1/2* *Fizz1* *Arg-1*
Cytokine secretion	TNF IL-1beta IL-6 IL-12 IL-23	IL-10 TGF-beta IL-1ra
Chemokine secretion	CCL10 CCL11 CCL5 CCL8 CCL9 CCL2 CCL3 CCL4	CCL17 CCL22 CCL24

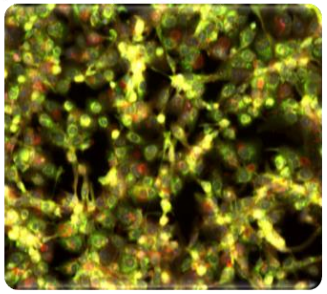
PHENOMICS

M1

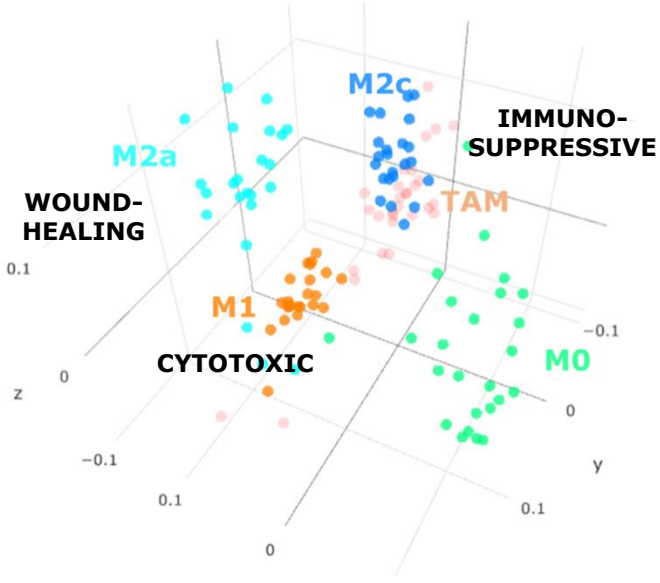


VS

M2a



FUNCTIONALLY RELEVANT CLUSTERING



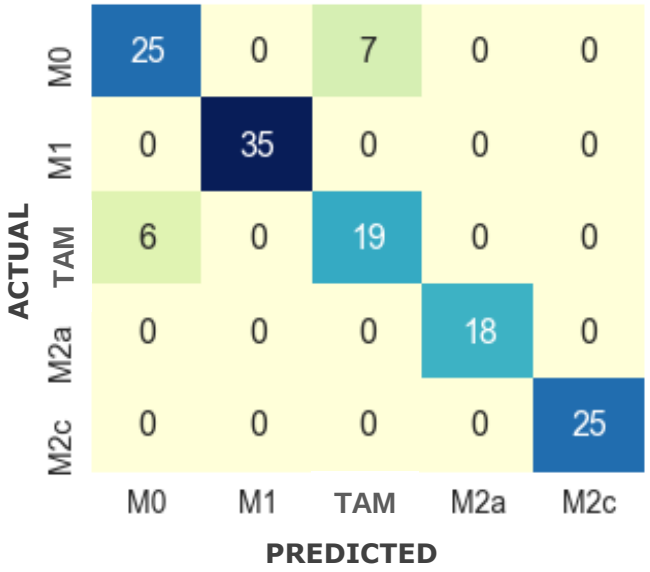
RECURSION

IMMUNO-ONCOLOGY DRUG DISCOVERY

MACHINE LEARNING IDENTIFIES NOVEL TAM MODULATORS

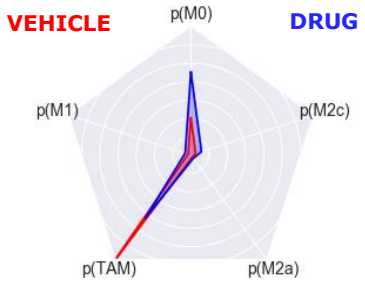
Machine learning combined with Recursion's proprietary biology platform can accomplish near perfect classification of complex macrophage polarizations and rapidly identify hits (to be validated) across polarization nodes reconciling ~1000 dimensional data.

MACHINE LEARNING CLASSIFIER

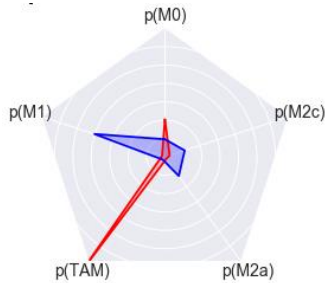


MULTI-NODAL DECONVOLUTION DELIVERS NOVEL TARGETS

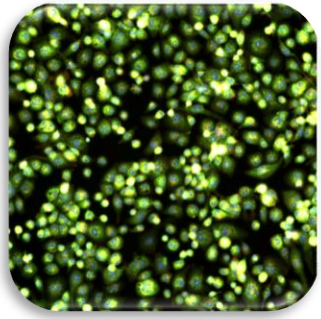
STAT3 INHIBITOR
TAM REVERSAL TO M0



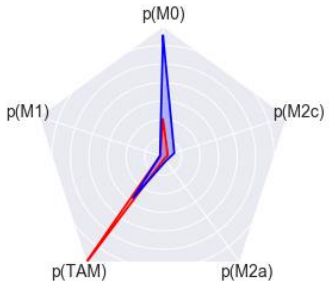
NOVEL TARGET-2
TAM SWITCH TO M1



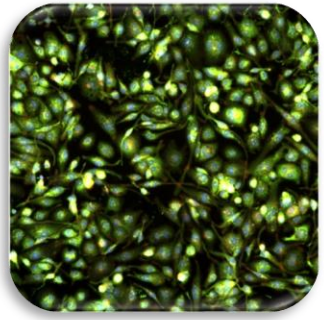
TAM (M-CSF)



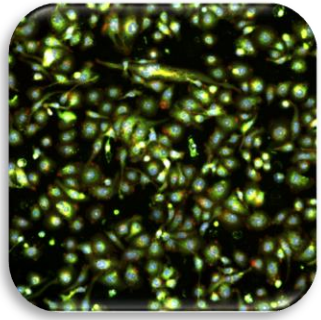
NOVEL TARGET-1
TAM REVERSAL TO M0



M1 (LPS + IFN)



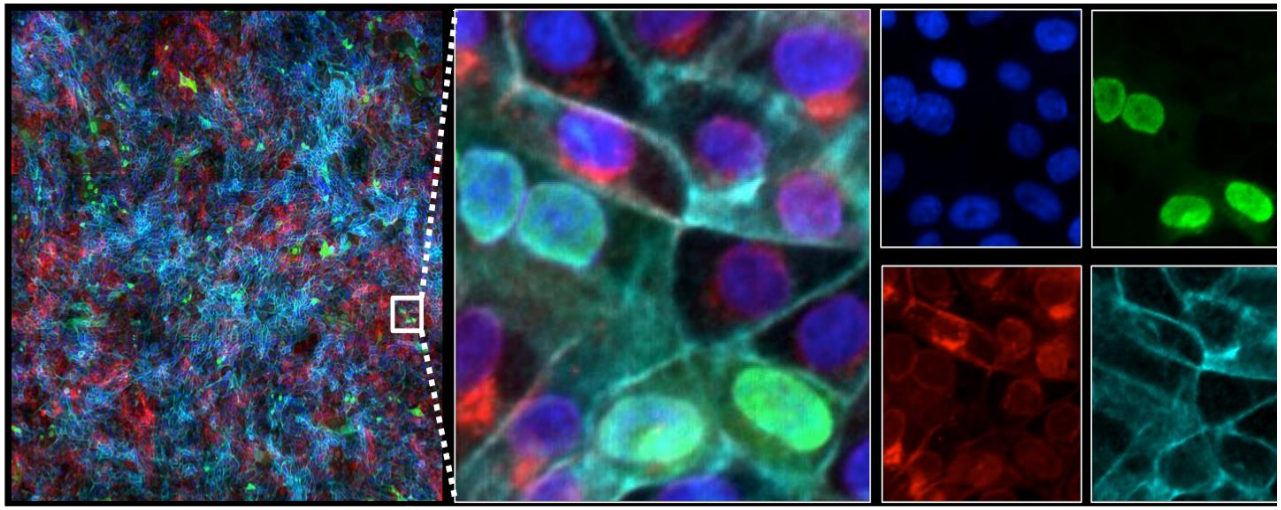
TAM + REC-2179

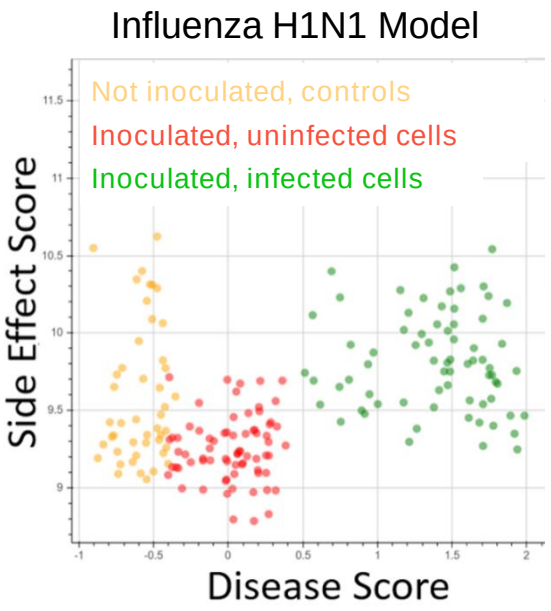


RECURSION

PHENOMICS ENABLED INFECTION MODELS
RAPID DEVELOPMENT AND SCREENING

Influenza infection yields distinct biological signatures of both directly infected and bystander cells detectable by Recursion's analytics platform. These robust models can be rapidly generated and scaled to enable high-throughput screening.

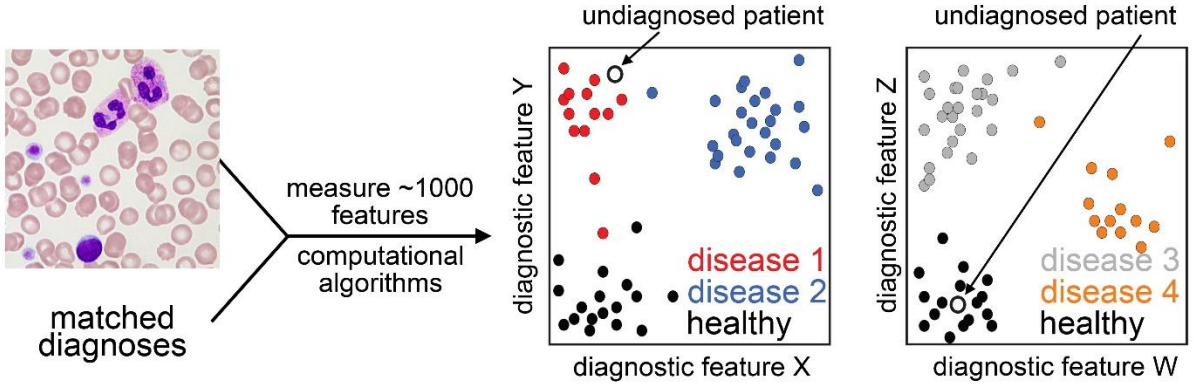


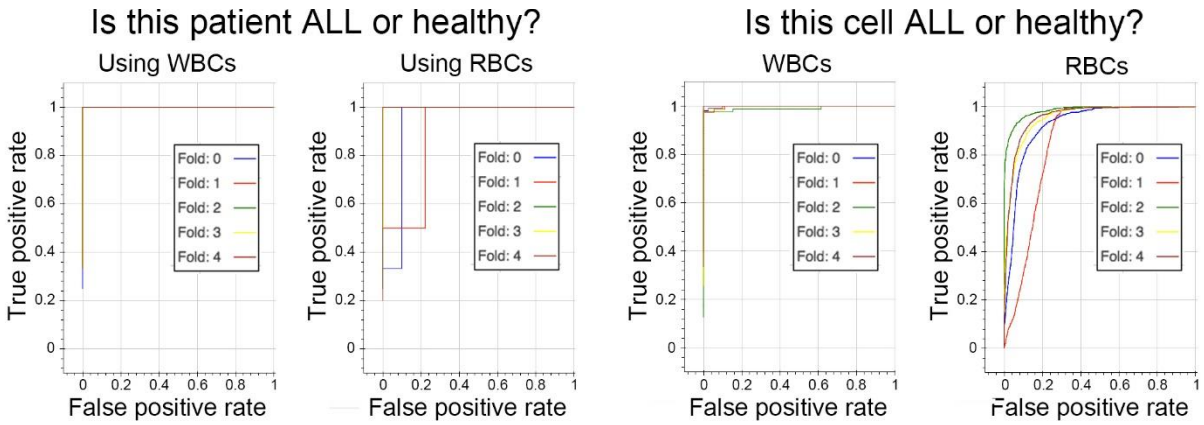


RECURSION

AI-ASSISTED DIAGNOSTICS
SUBTLE DISEASE-SPECIFIC FEATURES

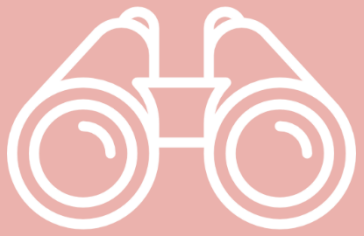
Complex morphological features of human hematopoietic cells can be interrogated with sophisticated AI methods to diagnose human diseases and sub-classify patients or complex conditions. Here, we are able to diagnose acute lymphoblastic leukemia (ALL) from images of white blood cells or even red blood cells, alone. These methods may be used to stratify responders and guide clinical trial decision-making.





RECURSION

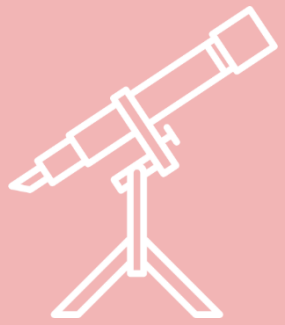
THE VISION



SHORT TERM

RARE GENETIC DISEASE

100+ genetic disease treatments by 2025



INTERMEDIATE TERM

EXPAND FOCUS

Disrupt drug discovery across new disease areas (aging, oncology, infectious disease) , and new applications (diagnostics, new chemical entity discovery)

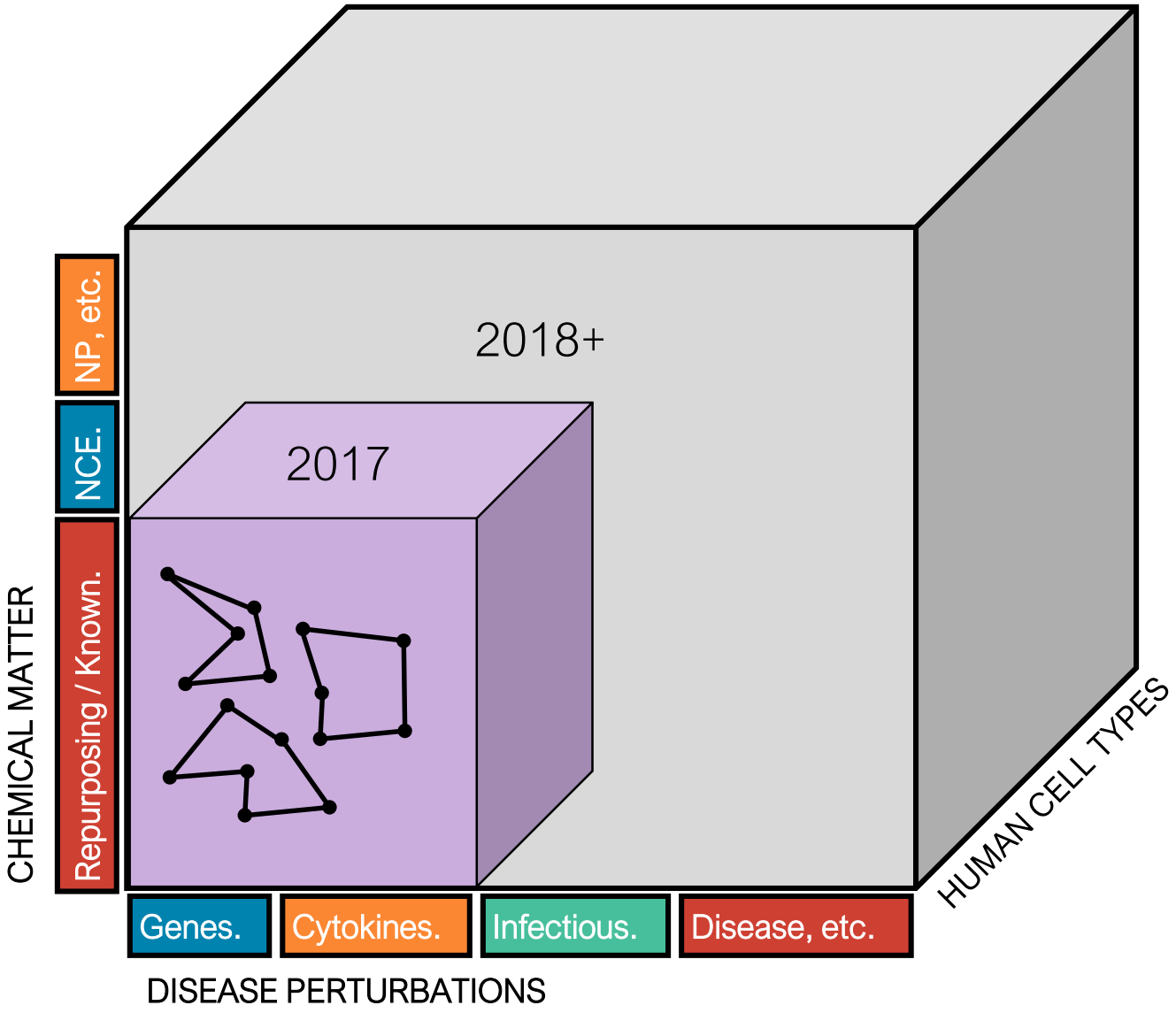
VISION

SYSTEMS BIOLOGY

Leverage technology to map most of human biology
-
Impact and monetization potential extreme

RECURSION

Toward a Map of Cellular Biology



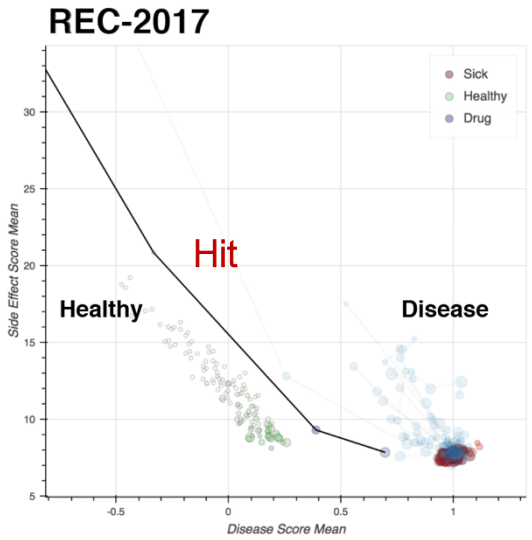
RECURSION

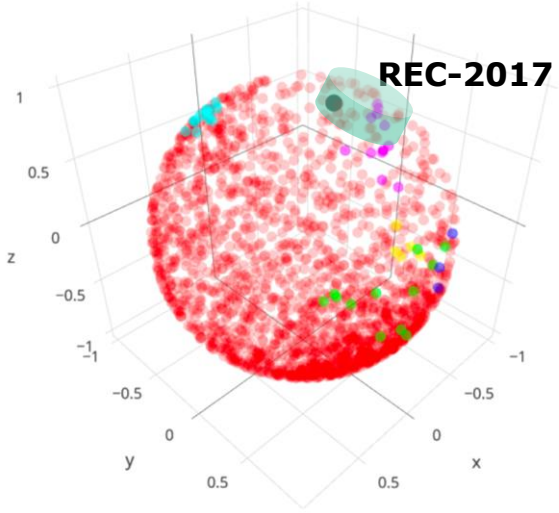
SMART LIBRARY CONSTRUCTION

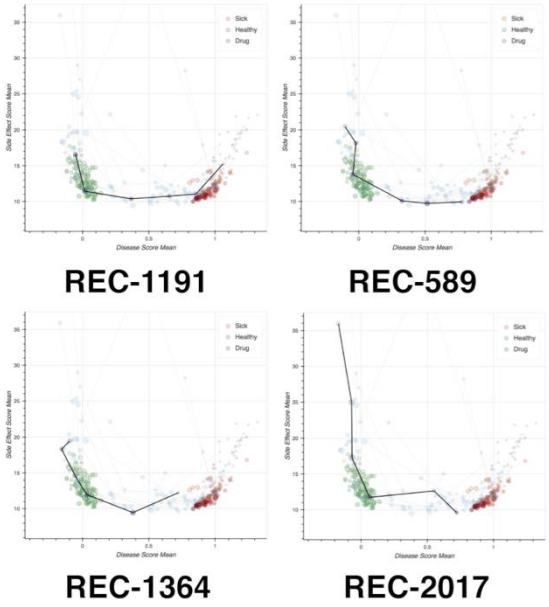
EFFICIENT CHEMICAL LIBRARIES

~90% smaller maximally diverse Smart Library of 'beacon' compounds created based on parent compound library phenotypic signatures to accelerate discovery and improve screening efficiency.

Smart Library hit → Recover similar compounds → Identify best in class or Drive SAR



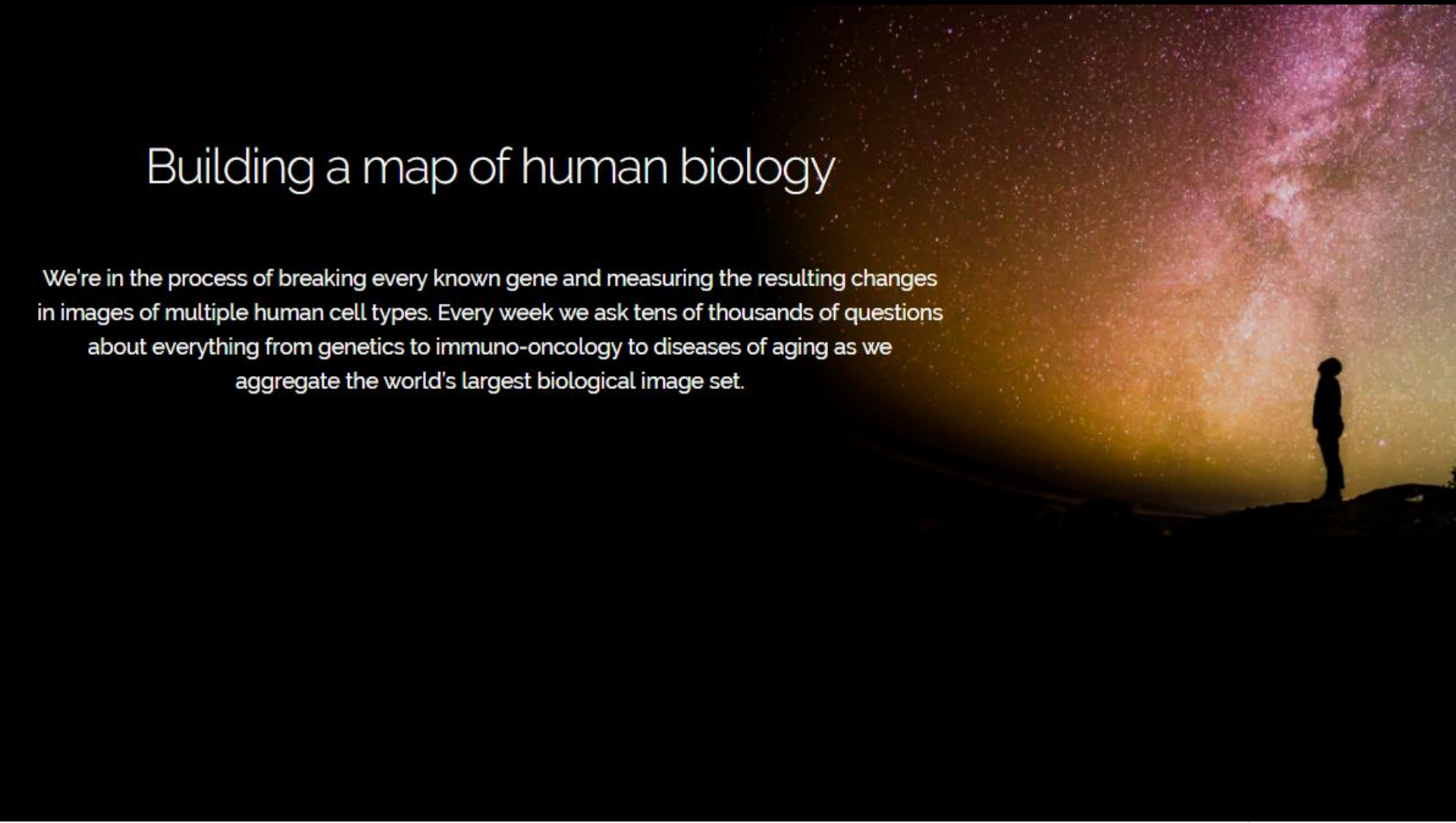




RECURSION

Building a map of human biology

We're in the process of breaking every known gene and measuring the resulting changes in images of multiple human cell types. Every week we ask tens of thousands of questions about everything from genetics to immuno-oncology to diseases of aging as we aggregate the world's largest biological image set.



PARTNERTING
OPPORTUNITIES

Therapeutic Repositioning

Identification of New Indications for Clinical Stage Shelved Assets or Indication Expansion of Marketed Assets Through Screening Across Dozens of Disease Models Per Year.

Target / Lead Discovery

NCE Lead Generation or Target Discovery across a Large Library of Disease Models Including: Genetic Diseases, Oncology, Inflammation.

Compound Intelligence

Characterization of Development Compounds Through Phenotypic Profiling to Reveal Pathways of Activity, Toxicity Profiles, among others.

RECURSION
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