24th Clinical Applications for Age Management Medicine

April 26-29, 2018

Omni Hotel & Resort, Championsgate/Orlando, Florida

ARTIFICIAL INTELLIGENCE FOR AGING BIOMARKERS & AGE MANAGEMENT RESEARCH

Age Management AMMG Medicine Group

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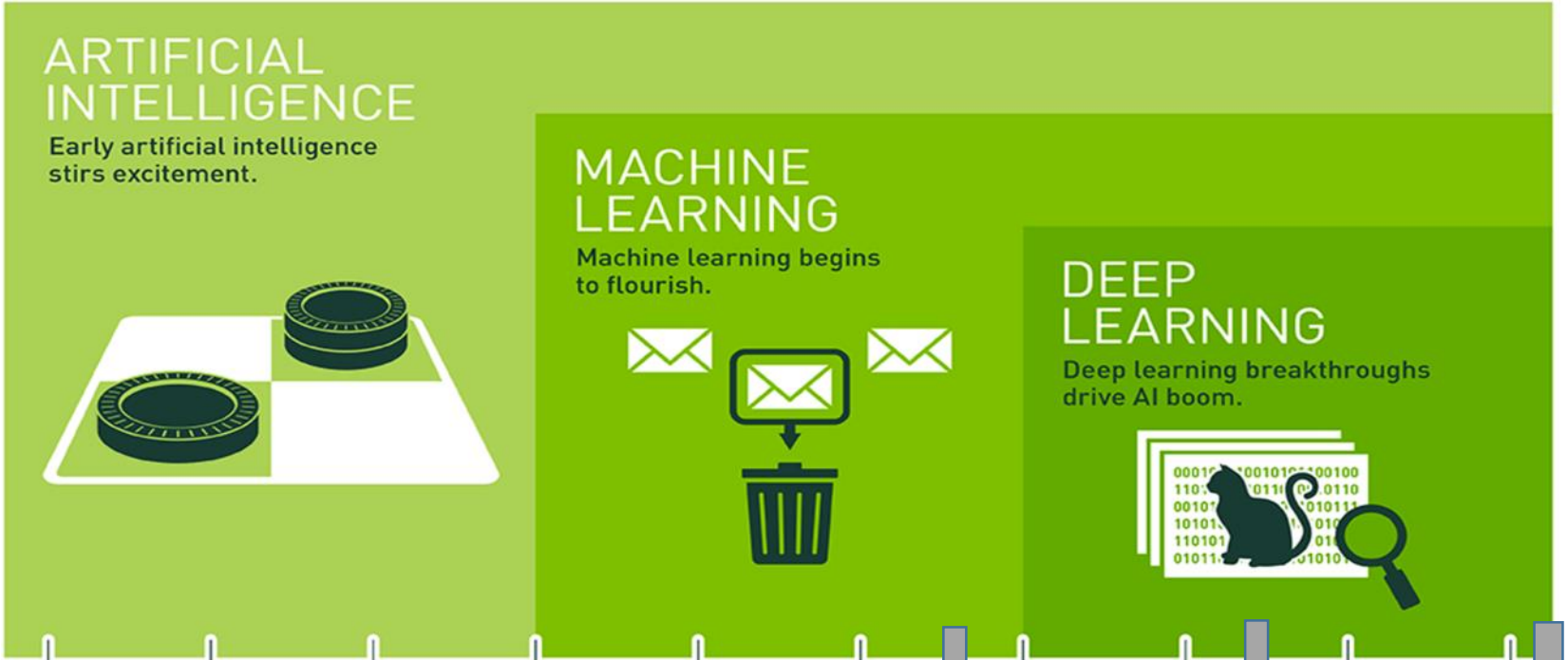
@biogerontology



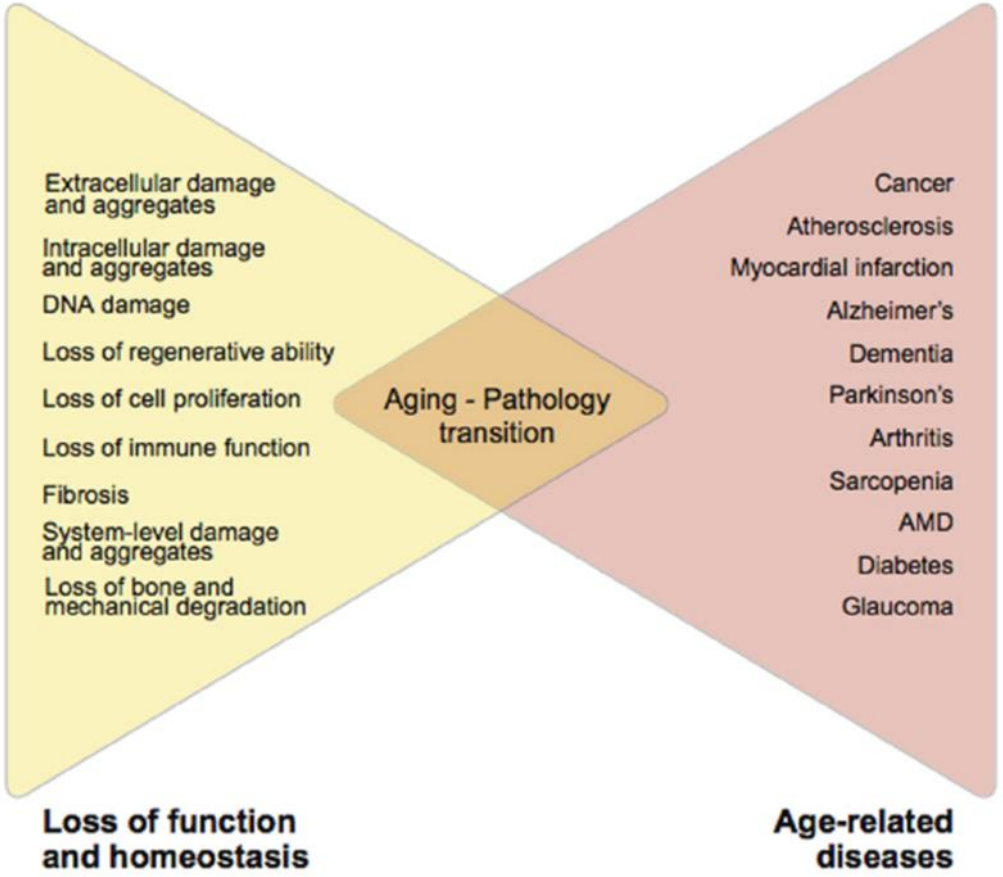
MOST OF THE "HYPE" IN AI IS DUE TO THE CREDIBLE ADVANCES IN DEEP LEARNING AND REINFORCEMENT LEARNING

IBM WATSON

DEEP LEARNING REVOLUTION

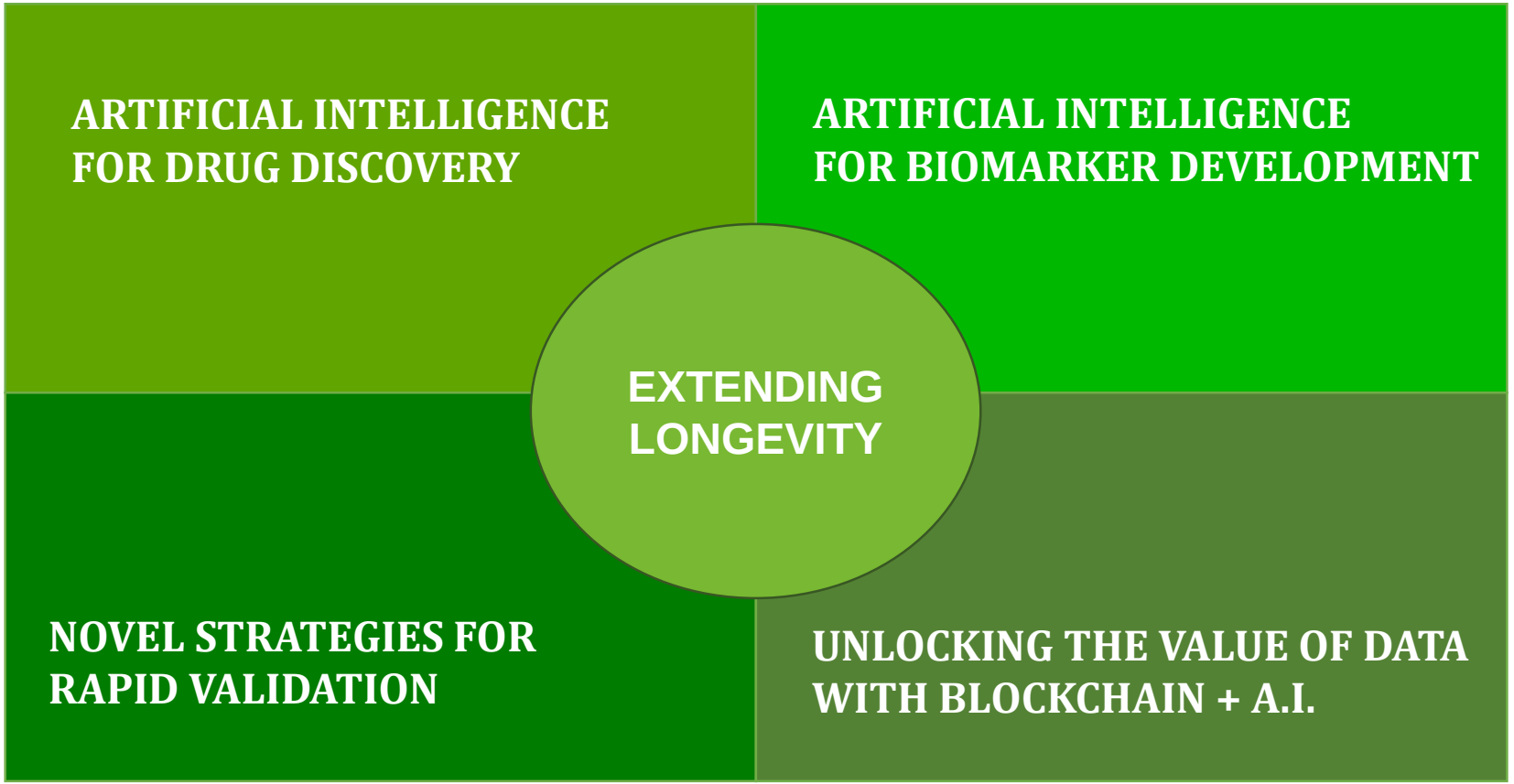
DEEP LEARNING REVOLUTION IN DRUG DISCOVERY

Source of the original image: nvidia.com



ARTIFICIAL INTELLIGENCE TO STUDY HUMAN AGING AND AGE-RELATED DISEASES TO IDENTIFY NOVEL MOLECULAR TARGETS AND TO DISCOVER NOVEL MOLECULES FOR THESE TARGETS

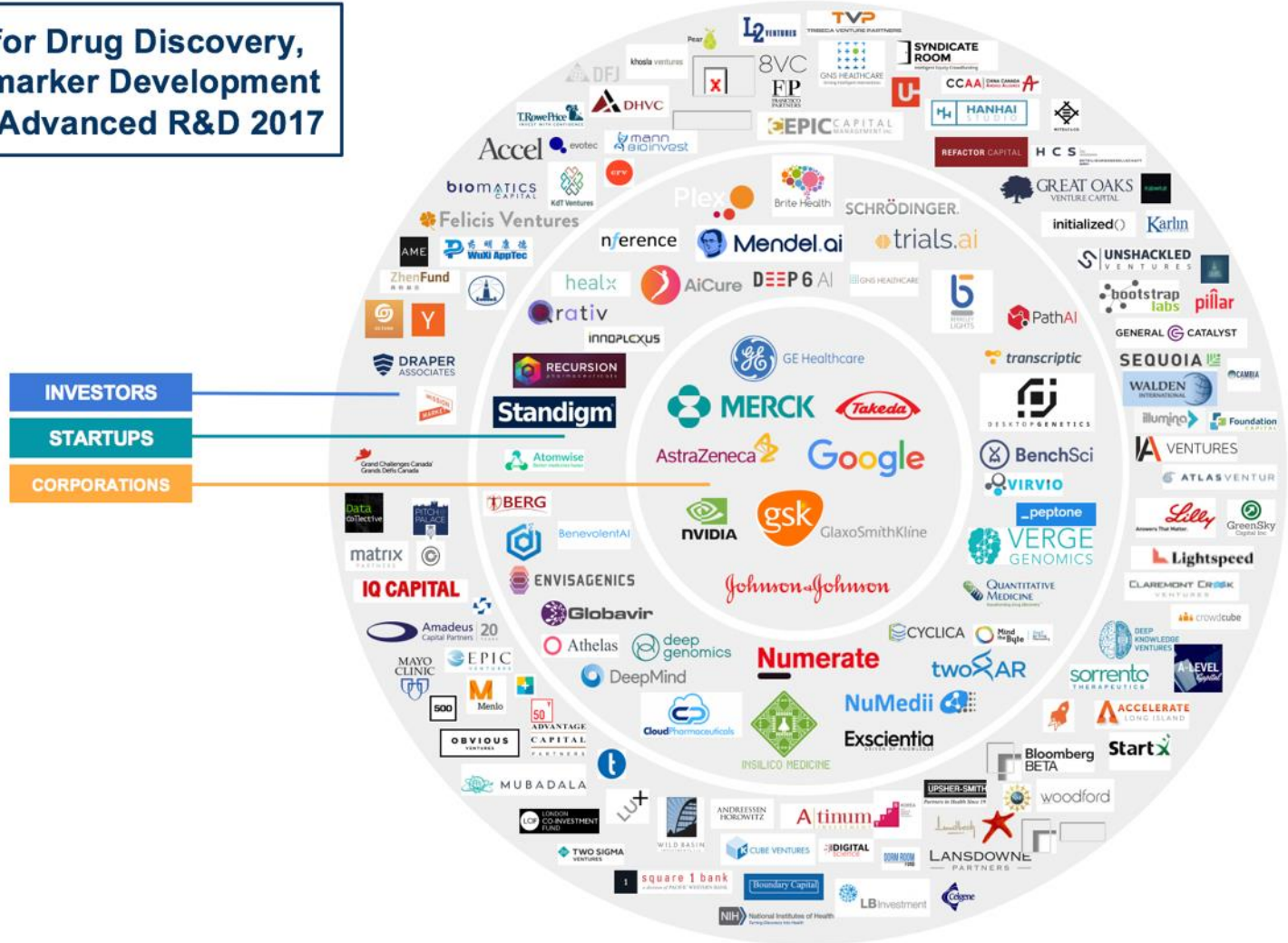
Zhavoronkov A and Bhullar B (2015) Classifying aging as a disease in the context of ICD-11.
Front. Genet. 6:326. doi: 10.3389/fgene.2015.00326


ARTIFICIAL INTELLIGENCE FOR DRUG DISCOVERY
ARTIFICIAL INTELLIGENCE FOR BIOMARKER DEVELOPMENT
EXTENDING LONGEVITY
NOVEL STRATEGIES FOR RAPID VALIDATION
UNLOCKING THE VALUE OF DATA WITH BLOCKCHAIN + A.I.

106 STARTUPS TRANSFORMING HEALTHCARE WITH AI



AI for Drug Discovery, Biomarker Development and Advanced R&D 2017



DEEP KNOWLEDGE VENTURES


CYBERSECURITY
ROBOTICS
FINTECH & INSURANCE
HARDWARE
ENDGAME.
DARKTRACE
cybereason
CROWDSTRIKE
OBSIDIAN
sparkcognition
Shift Technology
appthority
VERSIVE
SHAPE
perimeterx
vicarious
KINDRED
anki
UBTECH
brain corp
neurala
CloudMinds
GRAPHCORE
MYTHIC
Cerebras
Cambricon
zestfinance
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Upstart
Affirm
CAPE
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ENTERPRISE
HEALTHCARE
AUTO TECH
COMMERCE
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Osmo
HR TECH
mya
textio
workey
TRIFACTA
DataRobot
algolia
tamr
LEAPMIND
PETUUM
ELEMENT AI
freenome
babylon
RECURSION
INSILICO MEDICINE
TEMPUS
ARTERYS
AiCure
flatiron
Mighty AI
drive.ai
nauto
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Reflektion
Twiggle
aquifi
Cppier
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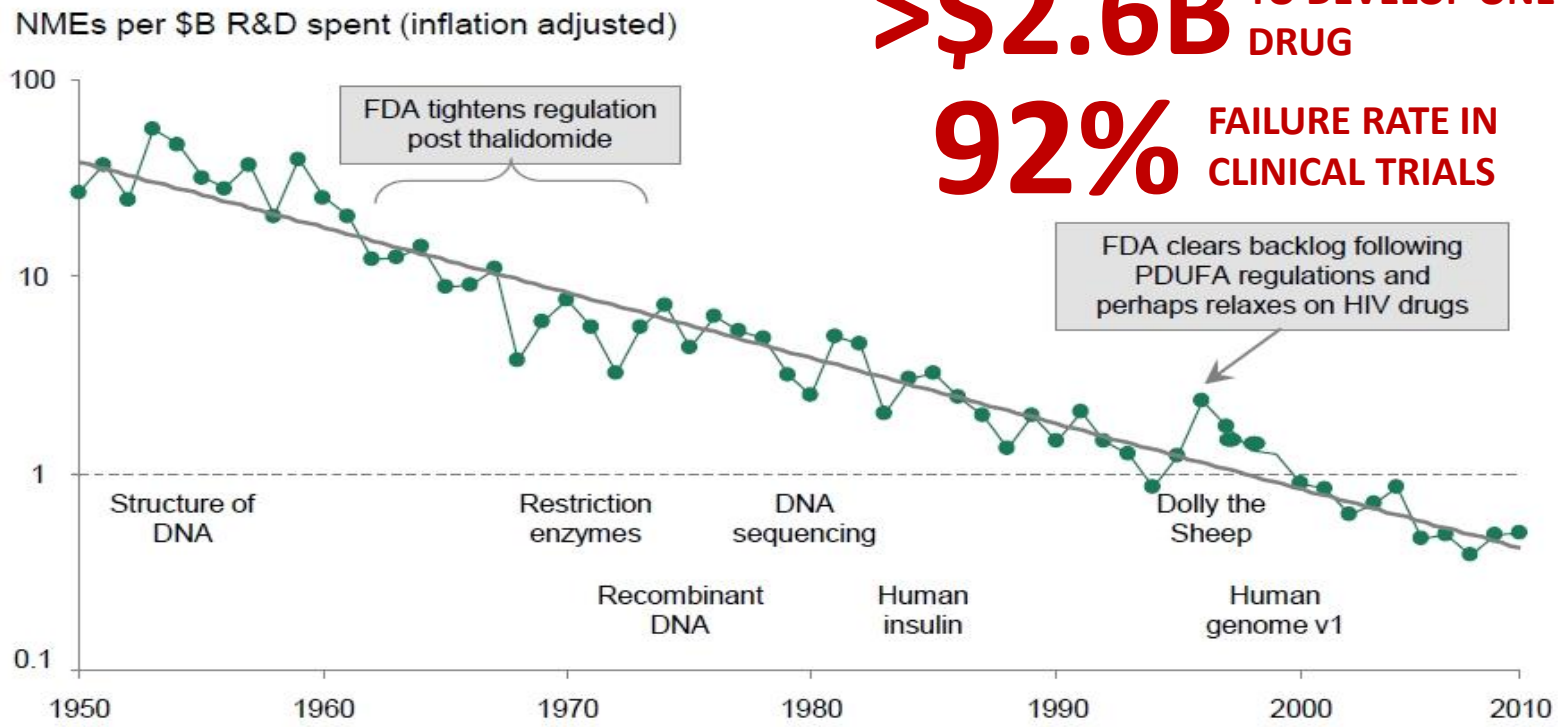
MARKETING, SALES, CRM
IOT
NEWS & MEDIA
BENSON-HILL
prospera
PHYSICAL SECURITY
SHIELD AI
Deep Sentinel
WorkFusion
SOCURE
onfido
text IQ
Merlin Intelligence
Amplero
INVOCA
Gong
afiniti
INSIDE SALES.COM
conversica
C3 IoT
MAANA
Preferred Networks
FOGHORN
ORCAM
SoundHound
BYTEDANCE
GEOSPATIAL ANALYTICS
Orbital Insight
Descartes Labs
LIFE SCIENCE
LEGAL TECH
IT & NETWORKS
SPORTS
ESPORTS
PERSONAL ASSISTANTS
TRAVEL
SOFTWARE DEVELOPMENT
zymergen
casetext
Moogsoft
SPORTLOGIQ
MOBALYTICS
sherpa
FLYR
applitools eyes

PHARMA EFFICIENCY IS DECLINING STEADILY

>$2.6B TO DEVELOP ONE DRUG

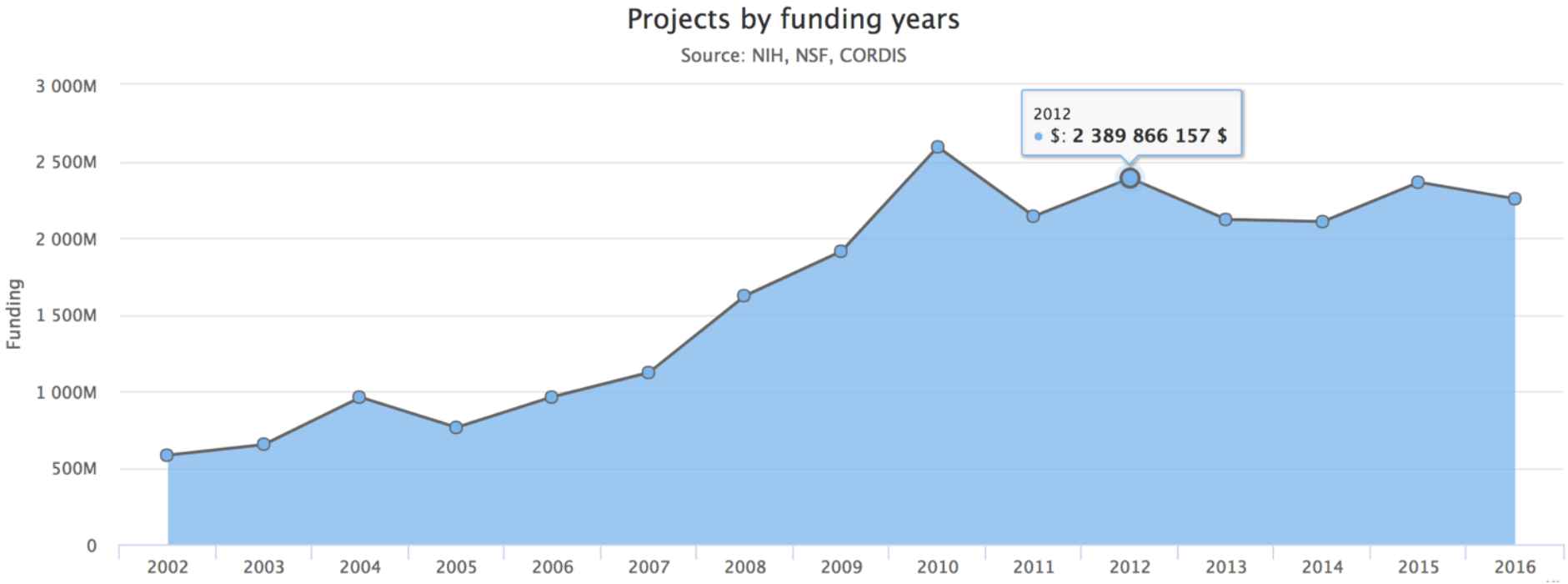
92% FAILURE RATE IN CLINICAL TRIALS



Bernstein Research: The Long View - R&D Productivity, 2010

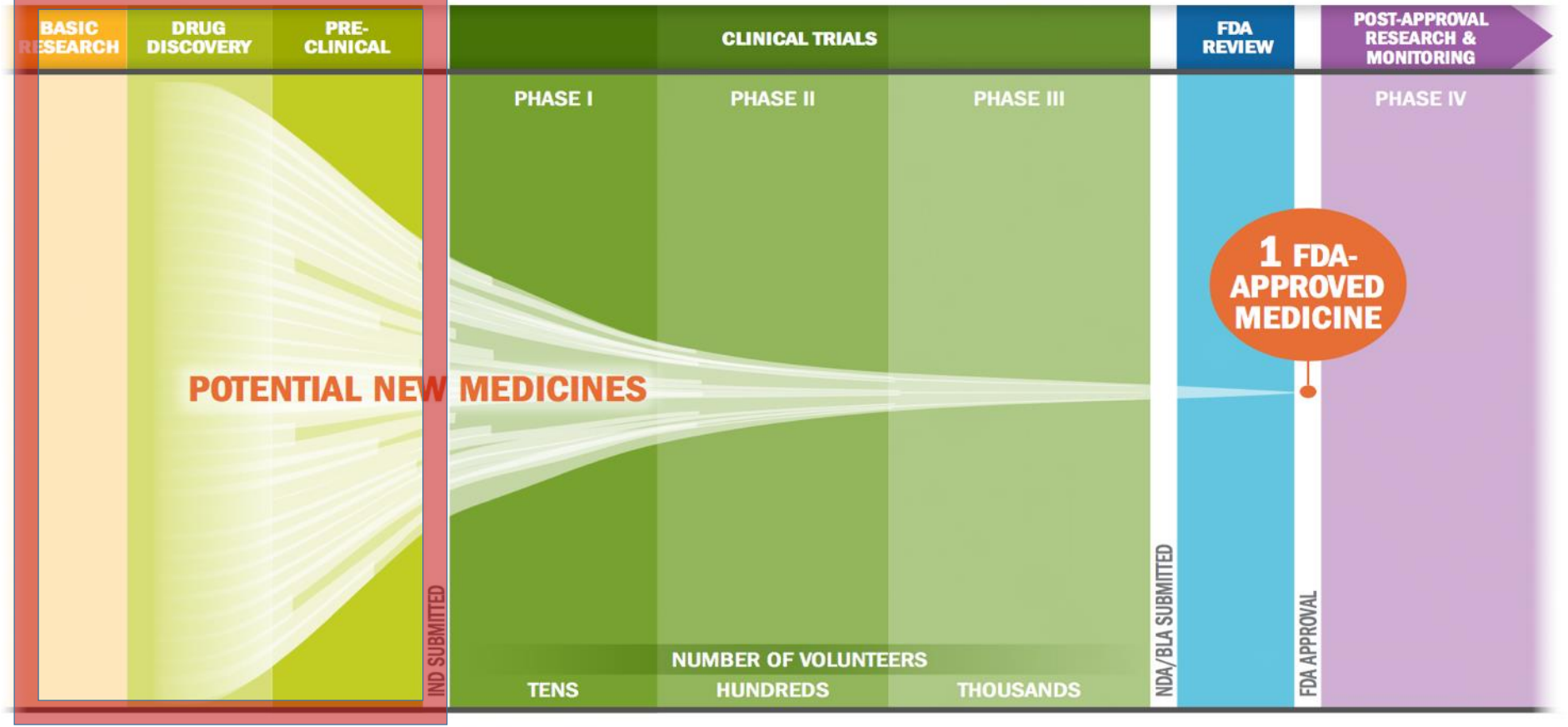
DOES NOT SHARE EVEN OLDEST DATA **46 NEW DRUGS launched in 2014**

OVER $20 BILLION IN PUBLIC FUNDING SPENT ON HIGH-THROUGHPUT EXPERIMENTS 1990-2010



SOURCE: PHARMACOGNITIVE.COM

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

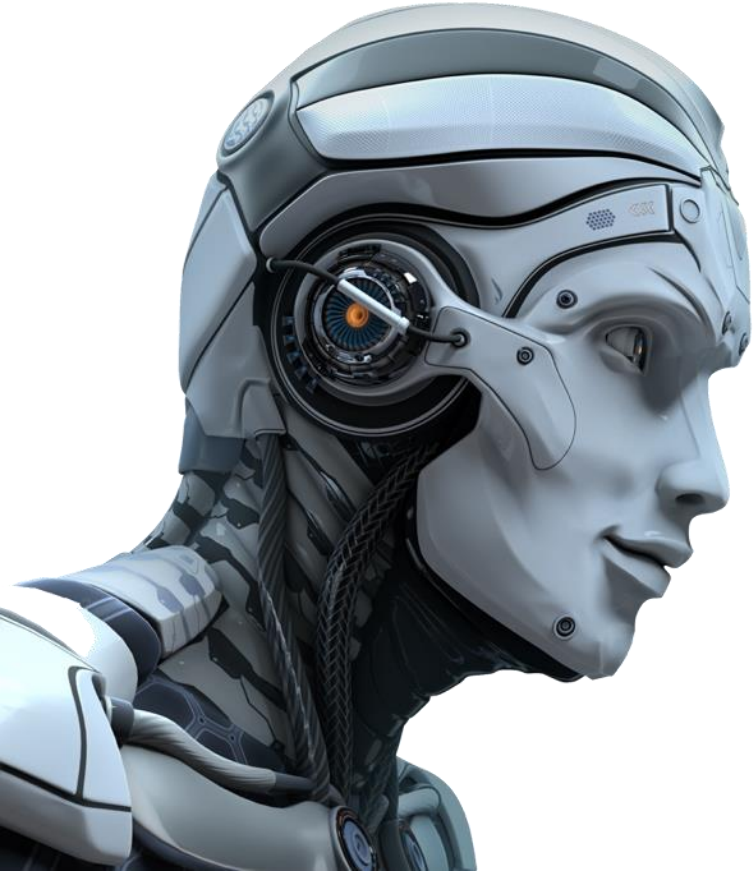


Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

Source: Biopharmaceutical Research & Development, PRMA http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

GLOBAL SALES: >$1 Trillion

GLOBAL R&D: >$150 Billion



>$2.6B TO DEVELOP ONE DRUG

92% FAILURE RATE IN CLINICAL TRIALS



WHAT MAKES A PERFECT MULTI-BILLION BLOCKBUSTER DRUG:

- CORRECT DISEASE TARGET
- SAFE (PHASE I) AND EFFECTIVE (PHASE II/III) MOLECULE
- MAJOR DISEASE

STRATEGIES FOR AI-POWERED DRUG DISCOVERY

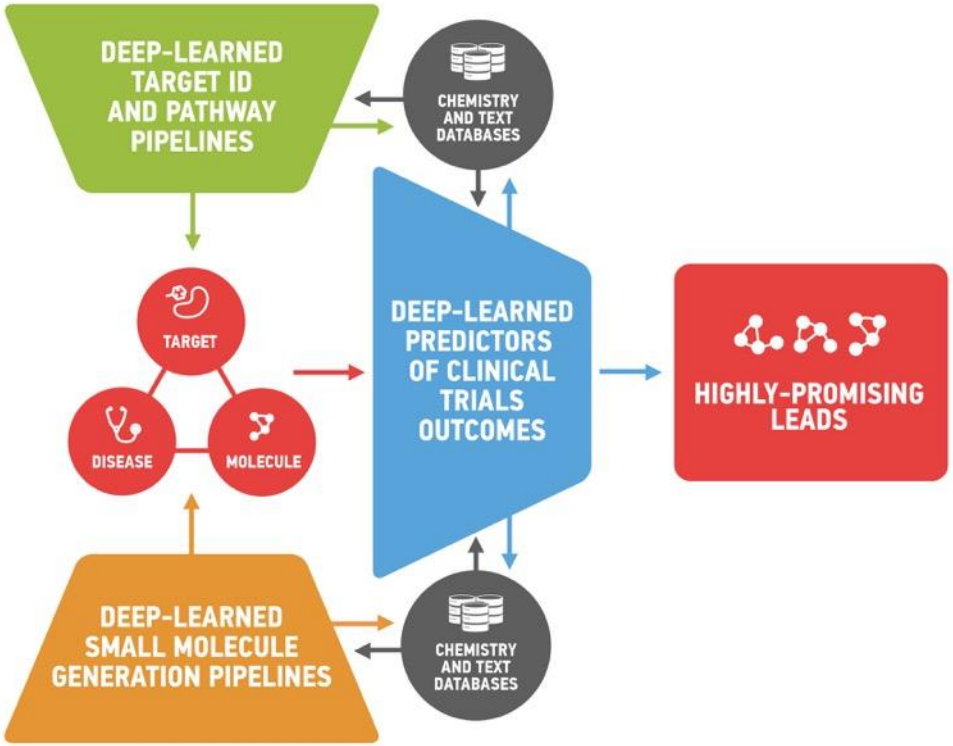


LOOKING FOR A NEEDLE IN A HAYSTACK

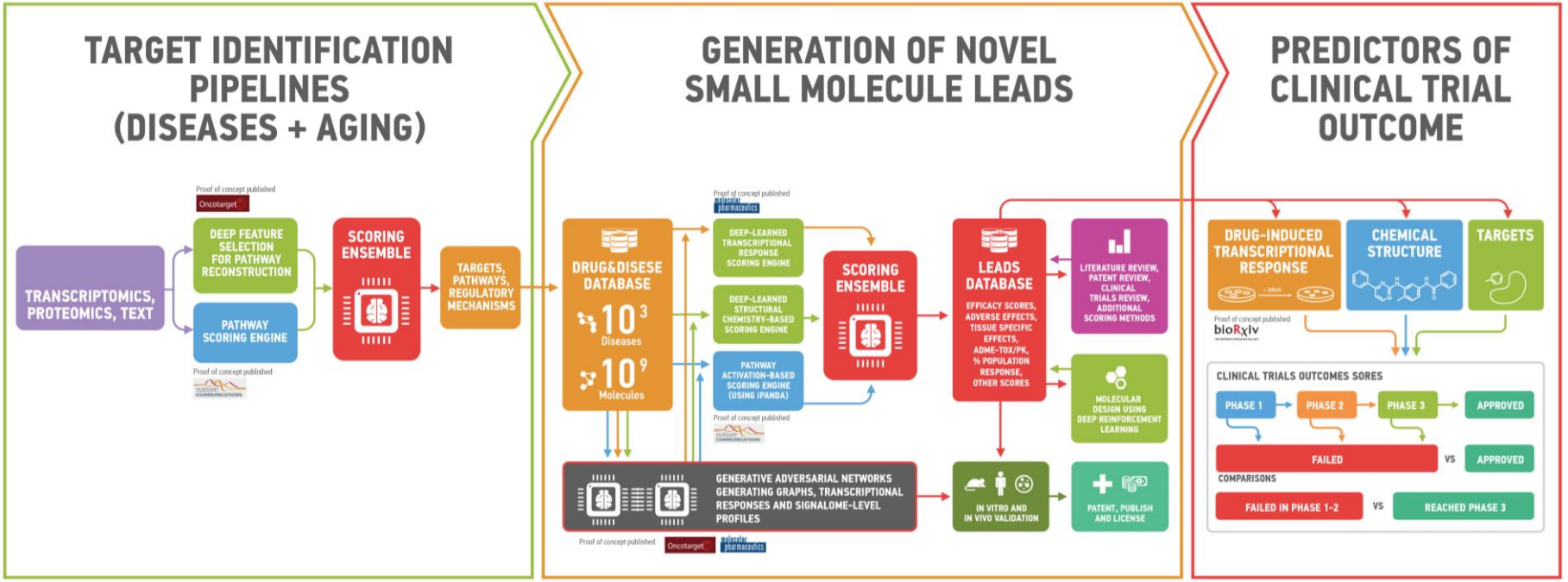


GENERATE PERFECT NEEDLES

INTEGRATED TOP-DOWN AND BOTTOM-UP TARGET ID AND DRUG DISCOVERY PIPELINES



COMPREHENSIVE END-TO-END DRUG DISCOVERY PIPELINE IN THE INDUSTRY UTILIZING NEXT-GENERATION ARTIFICIAL INTELLIGENCE



GAN/RL-BASED MOLECULAR GENERATORS WERE VALIDATED EXPERIMENTALLY AND ARE BEING FINE-TUNED

RESULTS WILL BE UNVEILED AT THE INTERNATIONAL CONFERENCE ON MACHINE LEARNING, JULY 10-15 2018

VALUATION OF A PRE-CLINICAL ASSET

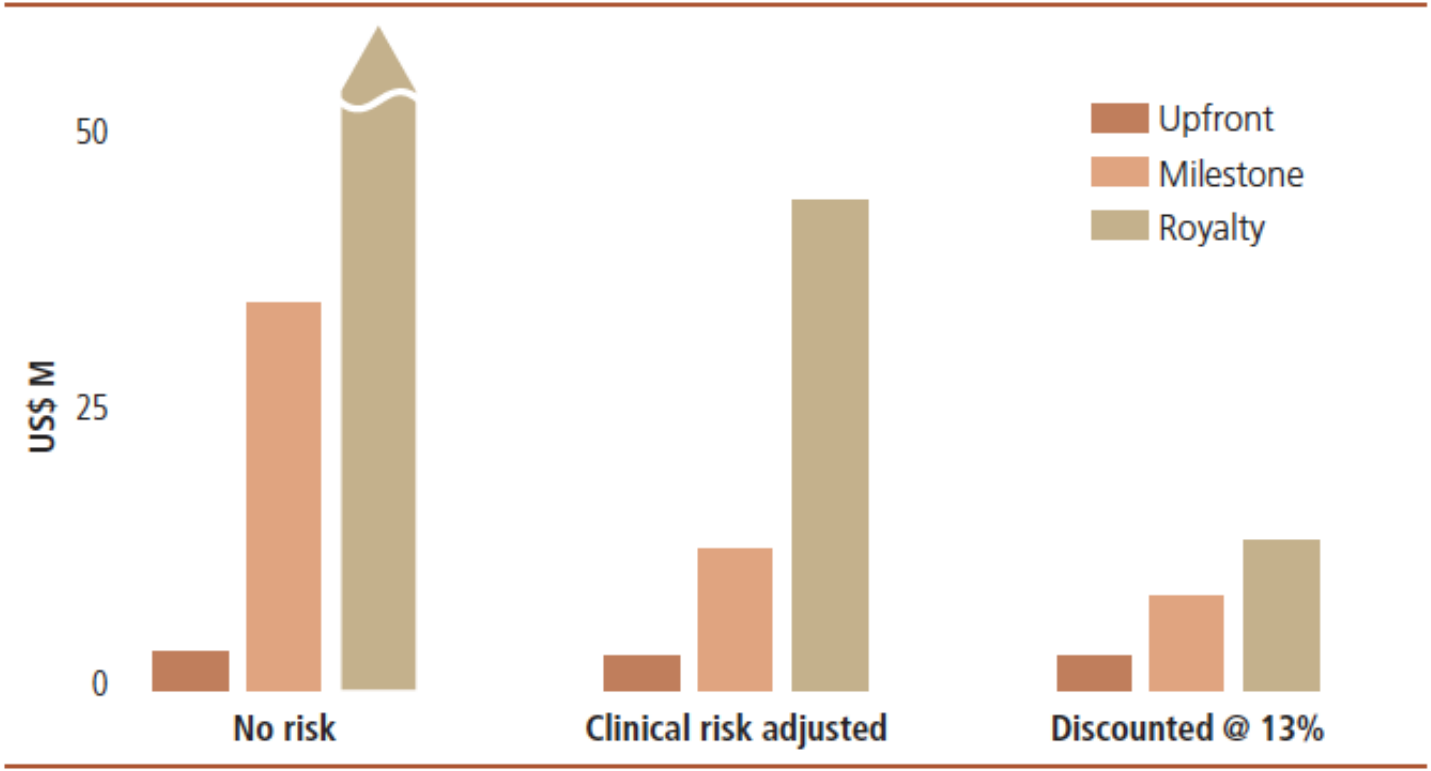


Figure 15 – The effect of time and risk on the value of deal components.

NEW BUSINESS MODELS EMERGE AS PHARMA STARTS TESTING THE DEEP LEANING WATERS

GEN News Highlights

More »

May 9, 2017

Sanofi, Exscientia Ink Up to €250M Deal for Bispecific Drugs Against Metabolic Diseases

Sanofi and Exscientia signed a potentially €250 million (approximately $273 million) collaboration and license option deal to discover bispecific small-molecule drugs against metabolic diseases. Scotland-based Exscientia will use its artificial intelligence (AI)-driven platform and automated design capabilities to identify combinations of synergistic drug targets, and then apply its lead-finding platform to identify bispecific small molecules against those targets.

Source: Genetic Engineering & Biotechnology News

FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

MedTech

GlaxoSmithKline taps Baltimore's Insilico for AI-based drug discovery

by *Amirah Al Idrus* | Aug 16, 2017 10:06am

GEN News Highlights

More »

June 12, 2017

Numerate to Use AI Platform in Developing Drugs for Takeda

Computational drug design company Numerate said today it will use its artificial intelligence (AI) platform to identify and deliver multiple clinical candidates for Takeda Pharmaceutical Company, through a collaboration whose value was not disclosed.

GEN News Highlights

More »

July 5, 2017

GSK Launches Up-to-$43M AI-Focused Collaboration with Exscientia

GlaxoSmithKline (GSK) will use the artificial intelligence (AI)-enabled platform of Exscientia to develop new drugs, through a collaboration that could generate up to £33 million (about $43 million) in milestone payments for the British AI-focused drug discovery and design company.

STRATEGIES FOR AI-POWERED DRUG DISCOVERY



LOOKING FOR A NEEDLE IN A HAYSTACK



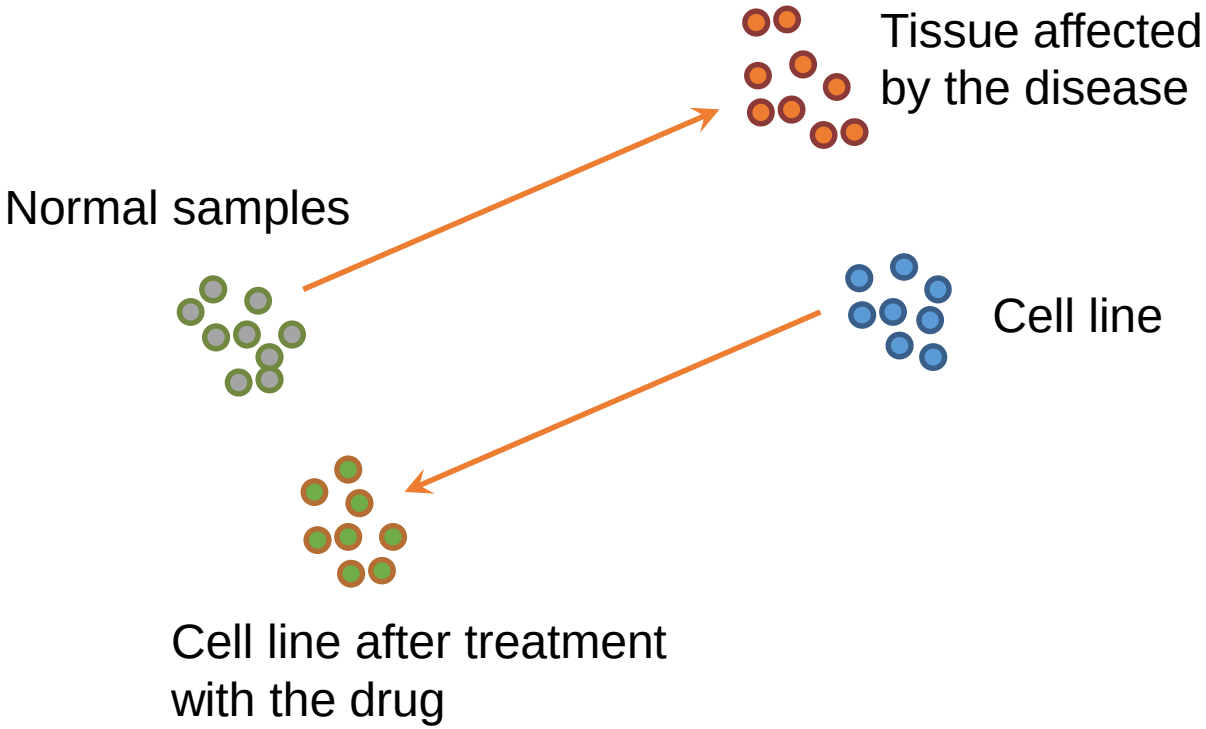
GENERATE PERFECT NEEDLES

STRATEGIES FOR AI-POWERED DRUG DISCOVERY

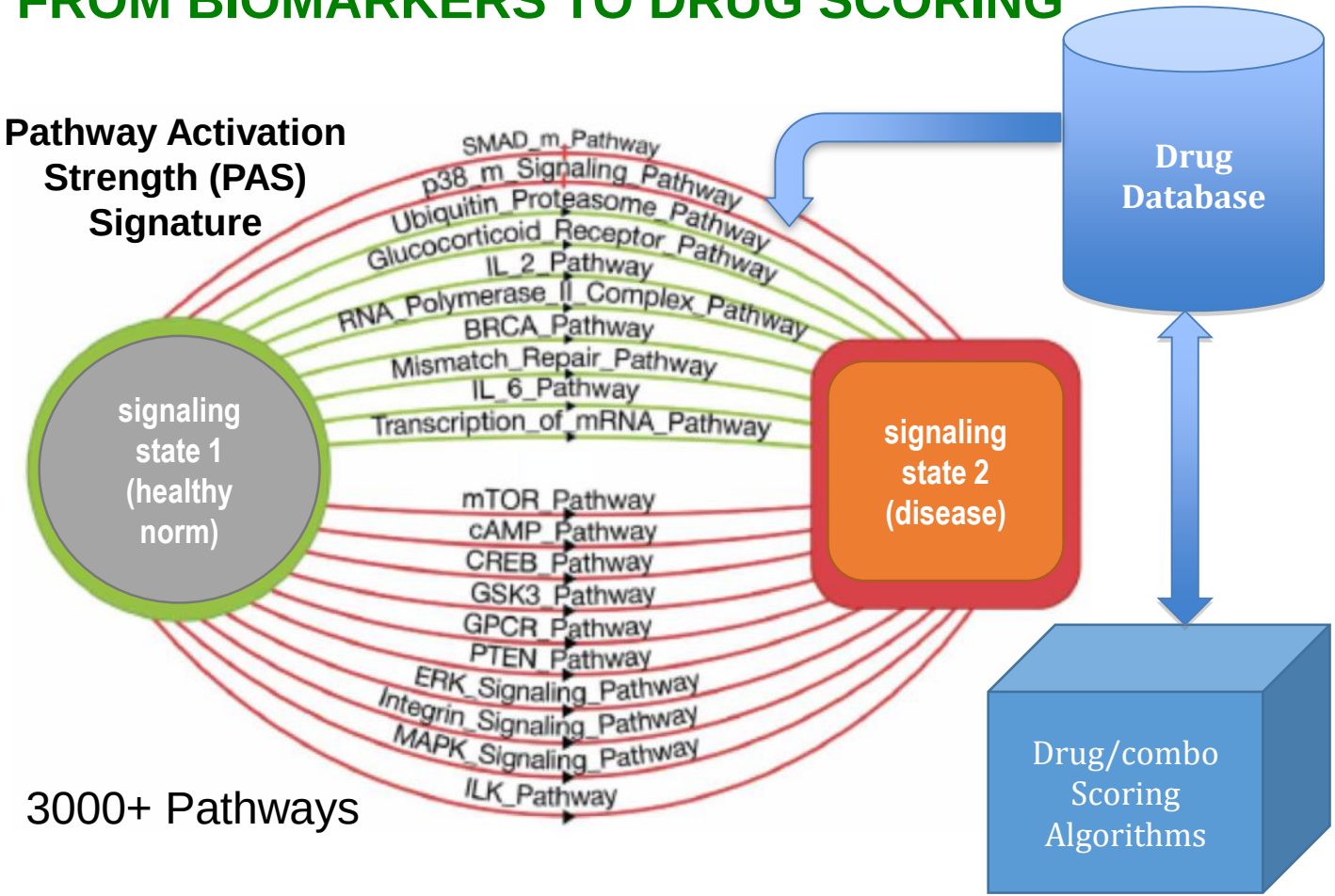


LOOKING FOR A NEEDLE IN A HAYSTACK

Transcriptome-based Drug scoring: general approach



FROM BIOMARKERS TO DRUG SCORING



CONSTRUCTING DISEASE SIGNATURES FROM BIG DATA

nature COMMUNICATIONS

ARTICLE

Received 7 Mar 2016 | Accepted 3 Oct 2016 | Published 16 Nov 2016

DOI: 10.1038/ncomms13427 OPEN

In silico Pathway Activation Network Decomposition Analysis (iPANDA) as a method for biomarker development

Ivan V. Ozerov[1,*], Ksenia V. Lezhnina[1,*], Evgeny Izumchenko[2], Artem V. Artemov[1], Sergey Medintsev[1], Quentin Vanhaelen[1], Alexander Aliper[1,3], Jan Vijg[4], Andreyan N. Osipov[1,3], Ivan Labat[5], Michael D. West[5], Anton Buzdin[1,3,6], Charles R. Cantor[7], Yuri Nikolsky[1,8], Nikolay Borisov[1,3,6], Irina Irincheeva[9], Edward Khokhlovich[10], David Sidransky[2], Miguel Luiz Camargo[10] & Alex Zhavoronkov[1,3,11]

published on November 16th, 2016

CONSTRUCTING DISEASE SIGNATURES FROM BIG DATA

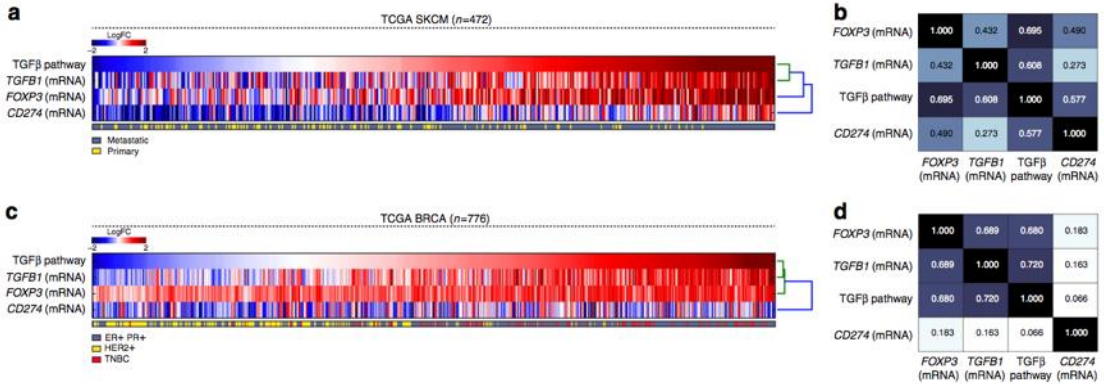
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-02696-6 OPEN

Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy

Rajani Ravi[1], Kimberly A. Noonan[2], Vui Pham[1], Rishi Bedi[3], Alex Zhavoronkov[4], Ivan V. Ozerov[4], Eugene Makarev[4], Artem V. Artemov[4], Piotr T. Wysocki[1], Ranee Mehra[5], Sridhar Nimmagadda[6], Luigi Marchionni[7], David Sidransky[1], Ivan M. Borrello[2], Evgeny Izumchenko[1] & Atul Bedi[1]



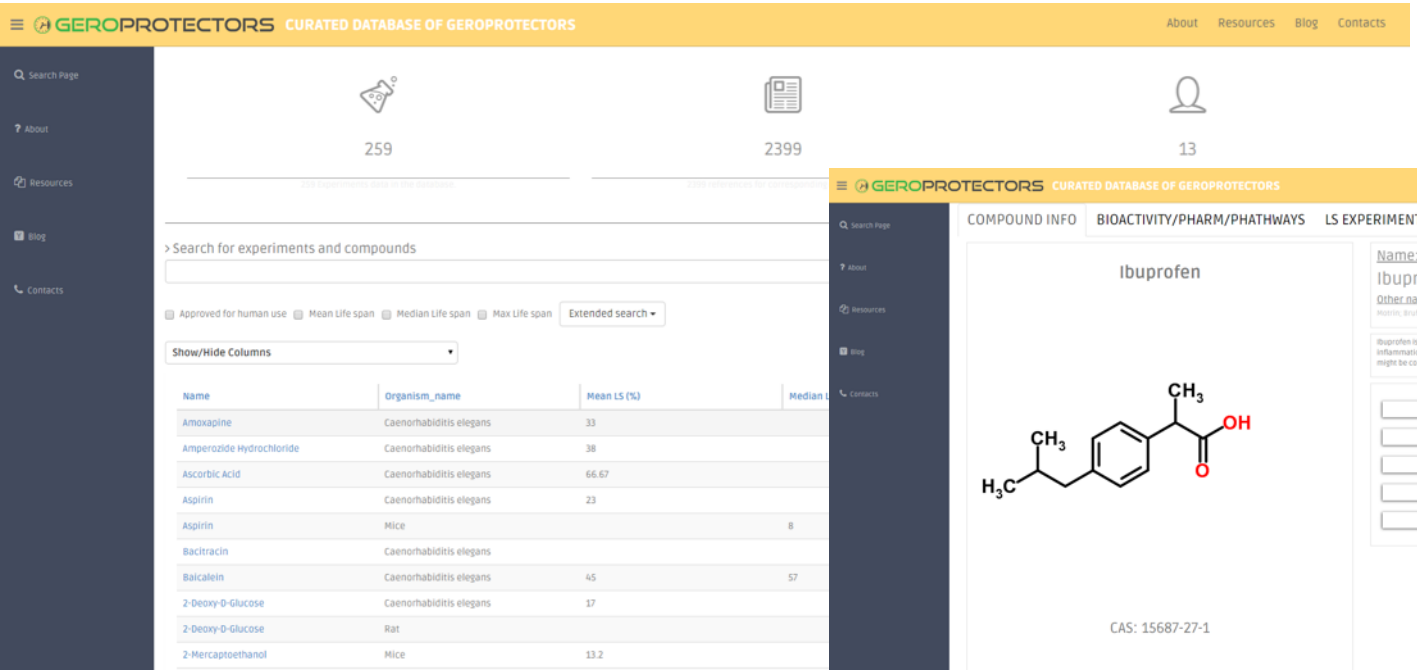
Published on February 21, 2018

www.impactaging.com AGING, September 2015, Vol 7 N 9

Research Paper

Geroprotectors.org: a new, structured and curated database of current therapeutic interventions in aging and age-related disease

Alexey Moskalev[1,2,3,4], Elizaveta Chernyagina[2], João Pedro de Magalhães[5,15], Diogo Barardo[5], Harikrishnan Thoppil[5], Mikhail Shaposhnikov[1], Arie Budovsky[6,16], Vadim E. Fraifeld[6], Andrew Garazha[2,7], Vasily Tsvetkov[2,8], Evgeny Bronovitsky[9], Vladislav Bogomolov[2], Alexei Scerbacov[10], Oleg Kuryan[10,11], Roman Gurinovich[10,11], Leslie C. Jellen[7,12], Brian Kennedy[13], Polina Mamoshina[7,15], Evgeniya Dobrovolskaya[1], Alex Aliper[7,14,15], Dmitry Kaminsky[15], and Alex Zhavoronkov[7,14,15]



www.aging-us.com AGING 2016, Vol. 8, No 9

Research Paper

In search for geroprotectors: in silico screening and *in vitro* validation of signalome-level mimetics of young healthy state

Alexander Aliper[1], Aleksey V. Belikov[2], Andrew Garazha[1,2,3], Leslie Jellen[1,4], Artem Artemov[1], Maria Suntsova[5], Alena Ivanova[5], Larisa Venkova[1,7], Nicolas Borisov[1,7], Anton Buzdin[7], Polina Mamoshina[1], Evgeny Putin[1], Andrew G. Swick[8], Alexey Moskalev[1, 2, 6, 9, 10], Alex Zhavoronkov[1, 11]

Correspondence to: Alex Zhavoronkov; **email:** alex@biogerontology.org
Keywords: geroprotector, drug discovery, screening, drug repurposing, aging
Received: April 23, 2016 **Accepted:** September 10, 2016 **Published:** September 24, 2016

ABSTRACT

Populations in developed nations throughout the world are rapidly aging, and the search for geroprotectors, or anti-aging interventions, has never been more important. Yet while hundreds of geroprotectors have extended lifespan in animal models, none have yet been approved for widespread use in humans. GeroScope is a computational tool that can aid prediction of novel geroprotectors from existing human gene expression data. GeroScope maps expression differences between samples from young and old subjects to aging-related signaling pathways, then profiles pathway activation strength (PAS) for each condition. Known substances are then screened and ranked for those most likely to target differential pathways and mimic the young signalome. Here we used GeroScope and shortlisted ten substances, all of which have lifespan-extending effects in animal models, and tested 6 of them for geroprotective effects in senescent human fibroblast cultures. PD-98059, a highly selective MEK1 inhibitor, showed both life-prolonging and rejuvenating effects. Natural compounds like N-acetyl-L-cysteine, Myricetin and Epigallocatechin gallate also improved several senescence-associated properties and were further investigated with pathway analysis. This work not only highlights several potential geroprotectors for further study, but also serves as a proof-of-concept for GeroScope, Oncofinder and other PAS-based methods in streamlining drug prediction, repurposing and personalized medicine.

www.aging-us.com AGING 2017, Vol. 9, Advance

Research Paper

Towards natural mimetics of metformin and rapamycin

Alexander Aliper[1], Leslie Jellen[1], Franco Cortese[2,3], Artem Artemov[1], Darla Karpinsky-Semper[4], Alexey Moskalev[5], Andrew G. Swick[4], Alex Zhavoronkov[1,2]

Correspondence to: Alexander Aliper; **email:** aliper@insilicomedicine.com
Keywords: geroprotector, metformin, rapamycin, deep learning, natural, nutraceutical, compound screening
Received: July 6, 2017 **Accepted:** November 2, 2017 **Published:** November 15, 2017

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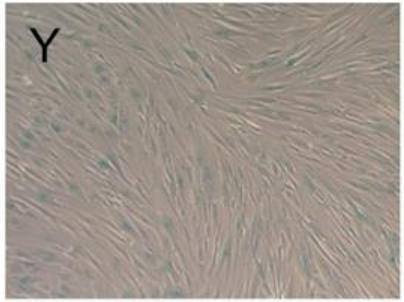
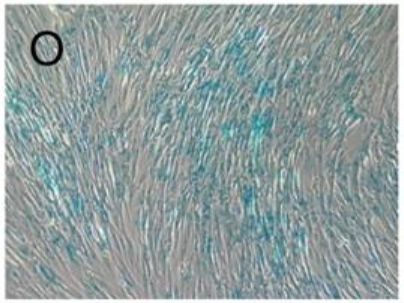
ABSTRACT

Aging is now at the forefront of major challenges faced globally, creating an immediate need for safe, widescale interventions to reduce the burden of chronic disease and extend human healthspan. Metformin and rapamycin are two FDA-approved mTOR inhibitors proposed for this purpose, exhibiting significant anti-cancer and anti-aging properties beyond their current clinical applications. However, each faces issues with approval for off-label, prophylactic use due to adverse effects. Here, we initiate an effort to identify nutraceuticals—safer, naturally-occurring compounds—that mimic the anti-aging effects of metformin and rapamycin without adverse effects. We applied several bioinformatic approaches and deep learning methods to the Library of Integrated Network-based Cellular Signatures (LINCS) dataset to map the gene- and pathway-level signatures of metformin and rapamycin and screen for matches among over 800 natural compounds. We then predicted the safety of each compound with an ensemble of deep neural network classifiers. The analysis revealed many novel candidate metformin and rapamycin mimetics, including allantoin and ginsenoside (metformin), epigallocatechin gallate and isoliquiritigenin (rapamycin), and withaferin A (both). Four relatively unexplored compounds also scored well with rapamycin. This work revealed promising candidates for future experimental validation while demonstrating the applications of powerful screening methods for this and similar endeavors.

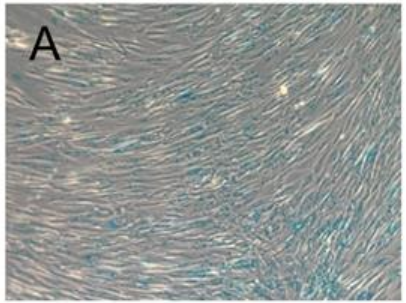
To verify the predictive potential of in silico models, the top substances rated by the program were added to non-transformed human embryonic lung fibroblasts at the senescence stage (“old”) in 50 μM concentrations and incubated for 3 days. Fibroblasts from several passages earlier, in a pre-senescent state (“young”) served as control.

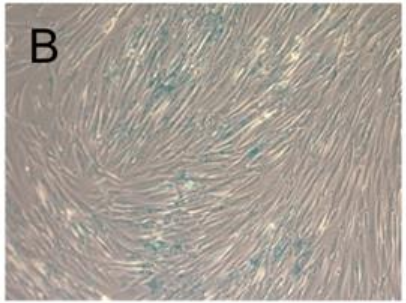
Cells	Substance	Code
young	-	Y
old	-	O
old	Nordihydroguaiaretic acid	A
old	Myricetin	B
old	N-acetyl-L-cysteine	G
old	Fasudil (HA-1077)	H
old	PD-98059	I
old	Epigallocatechin gallate	J

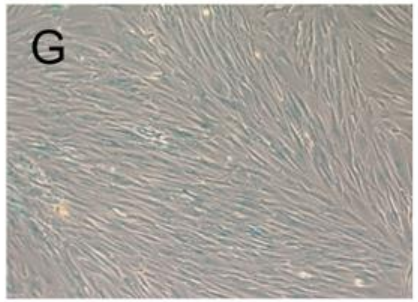


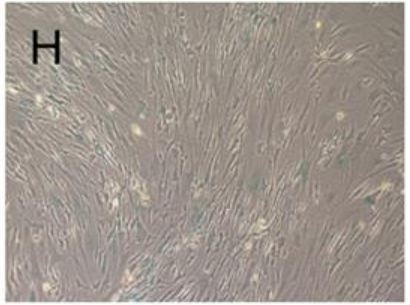


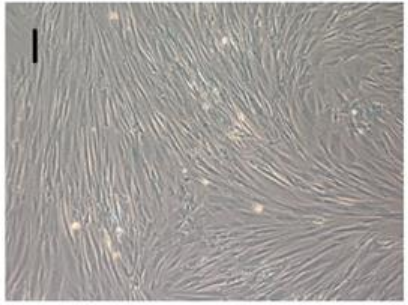
It can be seen that all substances, except A (nordihydroguaiaretic acid), strongly reduced beta-galactosidase staining of senescent fibroblasts.
Substance I (MEK inhibitor PD98059) had the most pronounced effect.

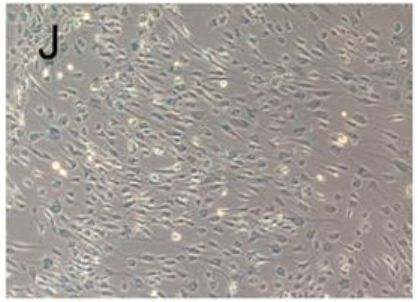












STRATEGIES FOR AI-POWERED DRUG DISCOVERY



GENERATE PERFECT NEEDLES

GENERATIVE ADVERSARIAL NETWORKS (GANs)

Computer Science > Neural and Evolutionary Computing

Generative Adversarial Text to Image Synthesis

Scott Reed, Zeynep Akata, Xinchen Yan, Lajanugen Logeswaran, Bernt Schiele, Honglak Lee

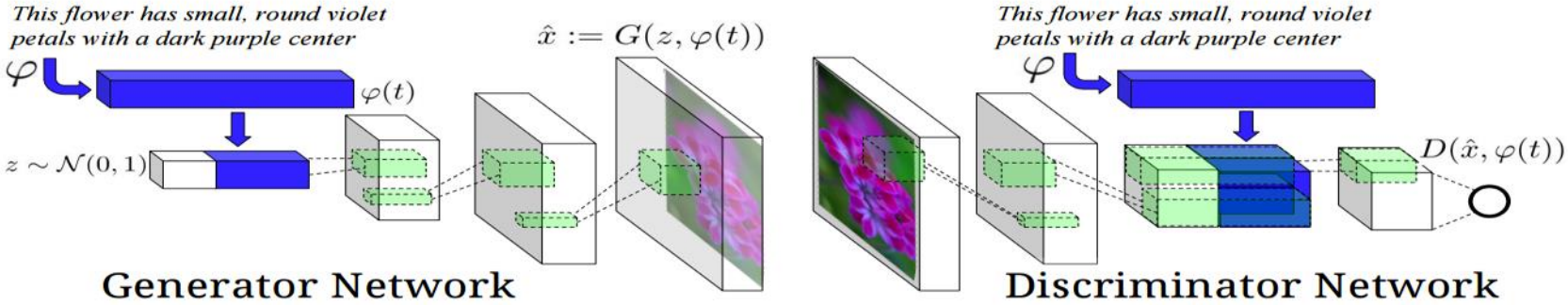
(Submitted on 17 May 2016 (v1), last revised 5 Jun 2016 (this version, v2))

Automatic synthesis of realistic images from text would be interesting and useful, but current AI systems are still far from this goal. However, in recent years generic and powerful recurrent neural network architectures have been developed to learn discriminative text feature representations. Meanwhile, deep convolutional generative adversarial networks (GANs) have begun to generate highly compelling images of specific categories, such as faces, album covers, and room interiors. In this work, we develop a novel deep architecture and GAN formulation to effectively bridge these advances in text and image model- ing, translating visual concepts from characters to pixels. We demonstrate the capability of our model to generate plausible images of birds and flowers from detailed text descriptions.

Comments: ICML 2016
Subjects: **Neural and Evolutionary Computing (cs.NE)**; Computer Vision and Pattern Recognition (cs.CV)
Cite as: arXiv:1605.05396 [cs.NE]
(or arXiv:1605.05396v2 [cs.NE] for this version)

Submission history

From: Scott Reed [view email]
[v1] Tue, 17 May 2016 23:09:15 GMT (2146kb,D)
[v2] Sun, 5 Jun 2016 13:39:27 GMT (2147kb,D)



this small bird has a pink breast and crown, and black primaries and secondaries.



this magnificent fellow is almost all black with a red crest, and white cheek patch.



the flower has petals that are bright pinkish purple with white stigma



this white and yellow flower have thin white petals and a round yellow stamen



Figure 1. Examples of generated images from text descriptions. Left: captions are from zero-shot (held out) categories, unseen text. Right: captions are from the training set.

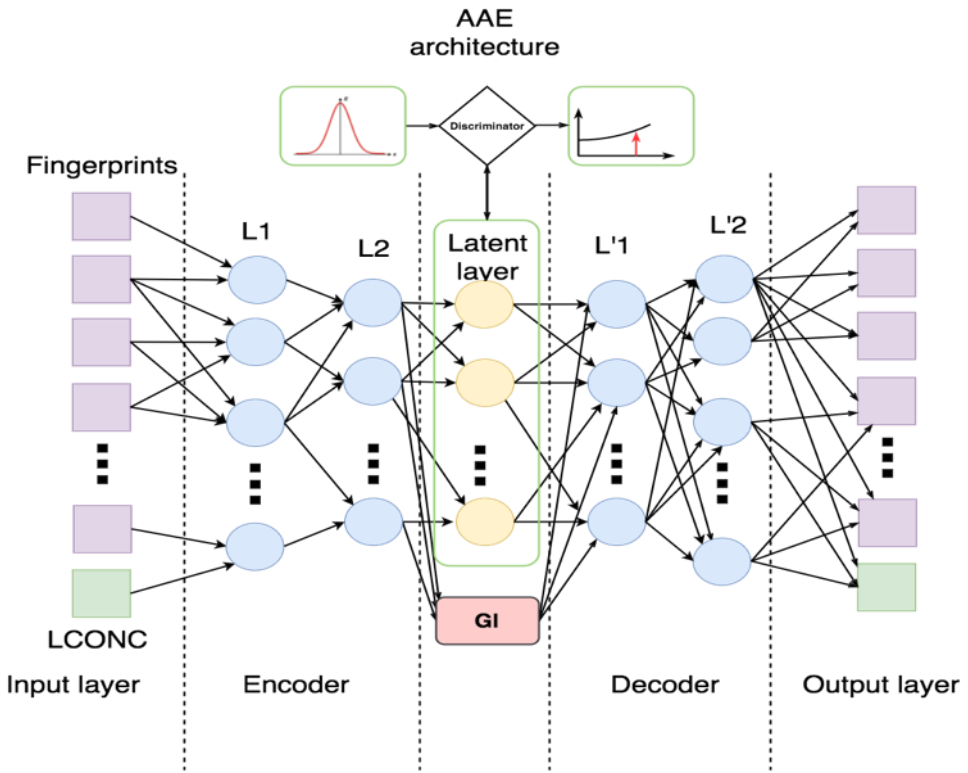
Reed et al, ICML 2016



Zhang et al, StackGAN: Text to Photo-realistic Image Synthesis with Stacked Generative Adversarial Networks

arXiv:1612.03242v1 [cs.CV] 10 Dec 2016

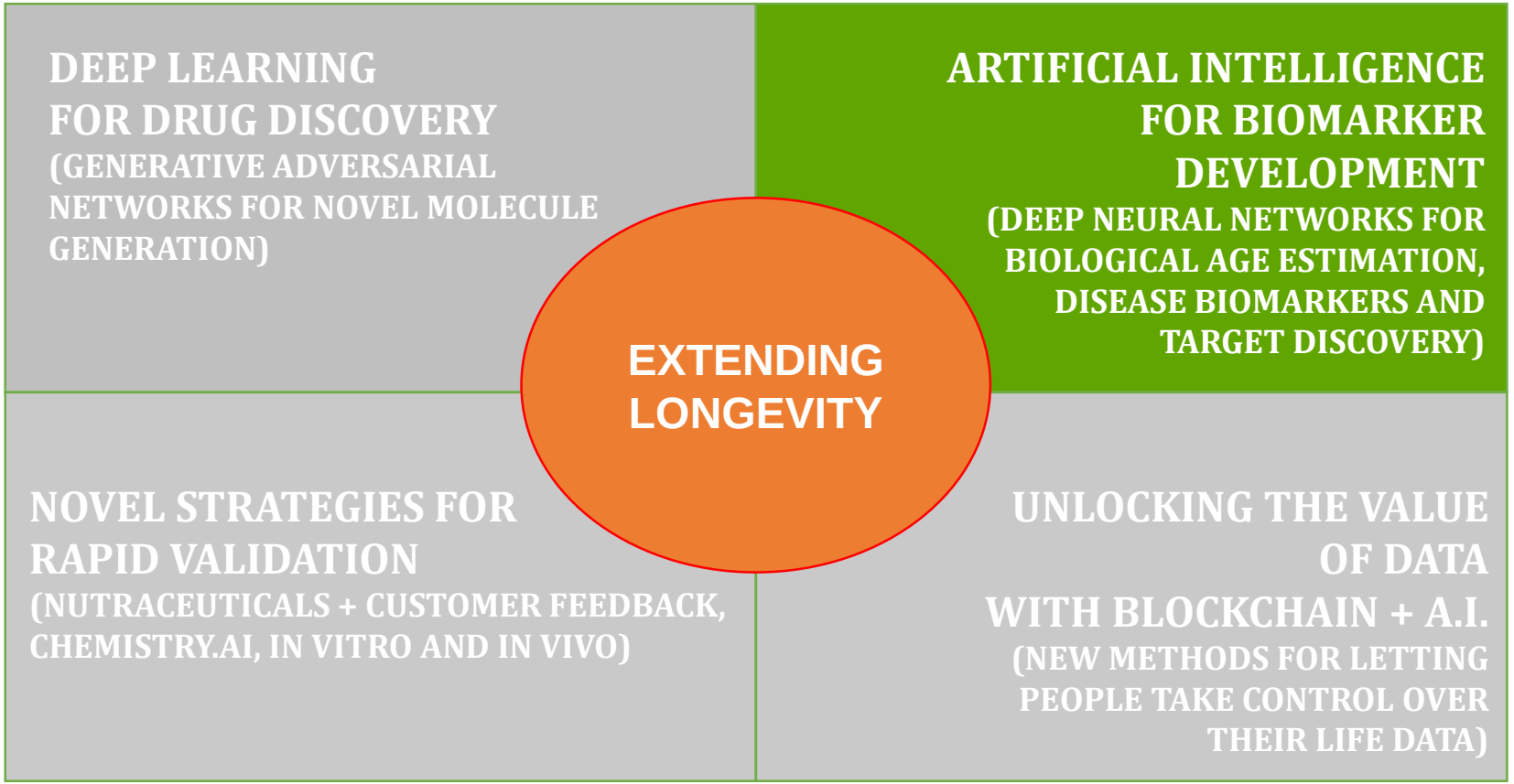
GANS AND REINFORCEMENT LEARNING FOR GENERATION OF THE PERFECT MOLECULES



source: Kadurin, et al, Oncotarget, December, 2016

**“HEY, DruGAN:
MAKE ME A MOLECULE
TO INHIBIT PROTEIN X
AT CONCENTRATION Y
WITH THE HIGHEST
BIOAVAILABILITY AND
THE MINIMAL SIDE
EFFECTS IN HUMANS”**

KEY ENABLING AND CONVERGING AREAS



NEW AI-POWERED LONGEVITY-FOCUSED PHARMA EMERGES



JUVENESCENCE
THE BOOK & THE COMPANY



Gregory Bailey, MD
Major investor in Medivation - >$14.5Billion



Jim Mellon
British "Warren Buffet"

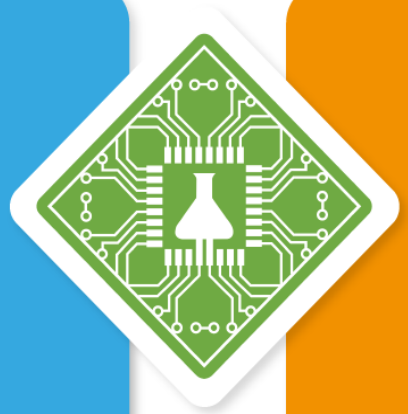


Declan Doogan, MD
developed Zoloft, Lipitor and Viagra

BRIDGING THE PHARMACEUTICAL AND CONSUMER INDUSTRIES

AI

DRUG DISCOVERY
BIOMARKER DEVELOPMENT
AGING RESEARCH
PERSONALIZED MEDICINE



BEAUTY
COSMETICS
NUTRITION
RECOMMENDATION ENGINES

HEALTH AND MEDICINE

CONSUMER INDUSTRY

Research Paper

In search for geroprotectors: in silico screening and *in vitro* validation of signalome-level mimetics of young healthy state

Alexander Aliper[1], Aleksey V. Belikov[2], Andrew Garazha[1,2,3], Leslie Jellen[1,4], Artem Artemov[1], Maria Suntsova[5], Alena Ivanova[5], Larisa Venkova[1,7], Nicolas Borisov[1,7], Anton Buzdin[7], Polina Mamoshina[1], Evgeny Putin[1], Andrew G. Swick[8], Alexey Moskalev[1, 2, 6, 9, 10], Alex Zhavoronkov[1, 11]

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[3]Center for Biogerontology and Regenerative Medicine, Moscow, 121099, Russia
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[6]Laboratory of Molecular Radiobiology and Gerontology, Institute of Biology of Komi Science Center of Ural Branch of Russian Academy of Sciences, Syktyvkar, 167982, Russia
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[9]School of Systems Biology, George Mason University (GMU), Fairfax, VA 22030, USA
[10]Engelhardt Institute of Molecular Biology of Russian Academy of Sciences, Moscow, 119991, Russia
[11]The Biogerontology Research Foundation, Oxford, UK

Correspondence to: Alex Zhavoronkov; **email:** alex@biogerontology.org
Keywords: geroprotector, drug discovery, screening, drug repurposing, aging
Received: April 23, 2016 **Accepted:** September 10, 2016 **Published:** September 24, 2016

ABSTRACT

Populations in developed nations throughout the world are rapidly aging, and the search for geroprotectors, or anti-aging interventions, has never been more important. Yet while hundreds of geroprotectors have extended lifespan in animal models, none have yet been approved for widespread use in humans. GeroScope is a computational tool that can aid prediction of novel geroprotectors from existing human gene expression data. GeroScope maps expression differences between samples from young and old subjects to aging-related signaling pathways, then profiles pathway activation strength (PAS) for each condition. Known substances are then screened and ranked for those most likely to target differential pathways and mimic the young signalome. Here we used GeroScope and shortlisted ten substances, all of which have lifespan-extending effects in animal models, and tested 6 of them for geroprotective effects in senescent human fibroblast cultures. PD-98059, a highly selective MEK1 inhibitor, showed both life-prolonging and rejuvenating effects. Natural compounds like N-acetyl-L-cysteine, Myricetin and Epigallocatechin gallate also improved several senescence-associated properties and were further investigated with pathway analysis. This work not only highlights several potential geroprotectors for further study, but also serves as a proof-of-concept for GeroScope, Oncofinder and other PAS-based methods in streamlining drug prediction, repurposing and personalized medicine.

Research Paper

Towards natural mimetics of metformin and rapamycin

Alexander Aliper[1], Leslie Jellen[1], Franco Cortese[2,3], Artem Artemov[1], Darla Karpinsky-Semper[4], Alexey Moskalev[5], Andrew G. Swick[4], Alex Zhavoronkov[1,2]

[1]Insilico Medicine, Inc, Research Department, Baltimore, MD 21218, USA
[2]Biogerontology Research Foundation, Research Department, Oxford, United Kingdom
[3]Department of Biomedical and Molecular Science, Queen's University School of Medicine, Queen's University, Kingston, ON K7L 3N6, Canada
[4]Life Extension, Ft. Lauderdale, FL 33308, USA
[5]Laboratory of Molecular Radiobiology and Gerontology, Institute of Biology of Komi Science Center of Ural Branch of Russian Academy of Sciences, Syktyvkar, 167982, Russia

Correspondence to: Alexander Aliper; **email:** aliper@insilicomedicine.com
Keywords: geroprotector, metformin, rapamycin, deep learning, natural, nutraceutical, compound screening
Received: July 6, 2017 **Accepted:** November 2, 2017 **Published:** November 15, 2017

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ABSTRACT

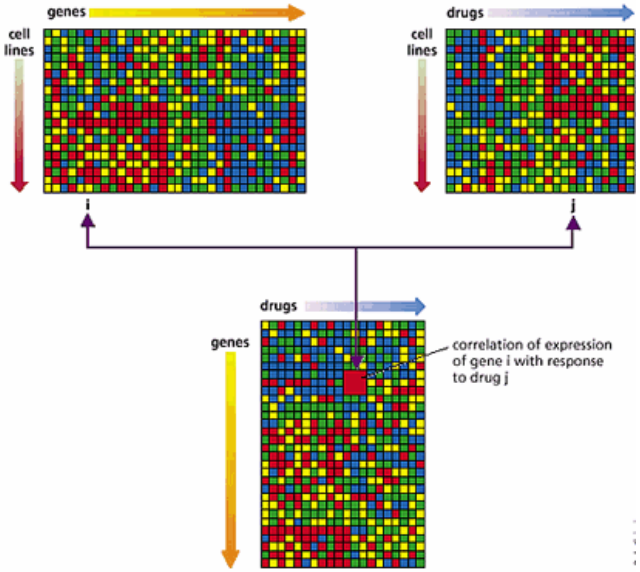
Aging is now at the forefront of major challenges faced globally, creating an immediate need for safe, widescale interventions to reduce the burden of chronic disease and extend human healthspan. Metformin and rapamycin are two FDA-approved mTOR inhibitors proposed for this purpose, exhibiting significant anti-cancer and anti-aging properties beyond their current clinical applications. However, each faces issues with approval for off-label, prophylactic use due to adverse effects. Here, we initiate an effort to identify nutraceuticals—safer, naturally-occurring compounds—that mimic the anti-aging effects of metformin and rapamycin without adverse effects. We applied several bioinformatic approaches and deep learning methods to the Library of Integrated Network-based Cellular Signatures (LINCS) dataset to map the gene- and pathway-level signatures of metformin and rapamycin and screen for matches among over 800 natural compounds. We then predicted the safety of each compound with an ensemble of deep neural network classifiers. The analysis revealed many novel candidate metformin and rapamycin mimetics, including allantoin and ginsenoside (metformin), epigallocatechin gallate and isoliquiritigenin (rapamycin), and withaferin A (both). Four relatively unexplored compounds also scored well with rapamycin. This work revealed promising candidates for future experimental validation while demonstrating the applications of powerful screening methods for this and similar endeavors.

WHY DO WE NEED MULTI-MODAL BIOMARKERS OF AGING IN PERSONALIZED MEDICINE?

PERSONALIZE THE THERAPY FOR INDIVIDUAL BIOLOGICAL AGE

IDENTIFY COMPANION THERAPIES TO INCREASE RESPONSE (E.G. MAJOR NEED IN IMMUNO ONCOLOGY)

Multi-staged longevity therapeutics: 5R strategy



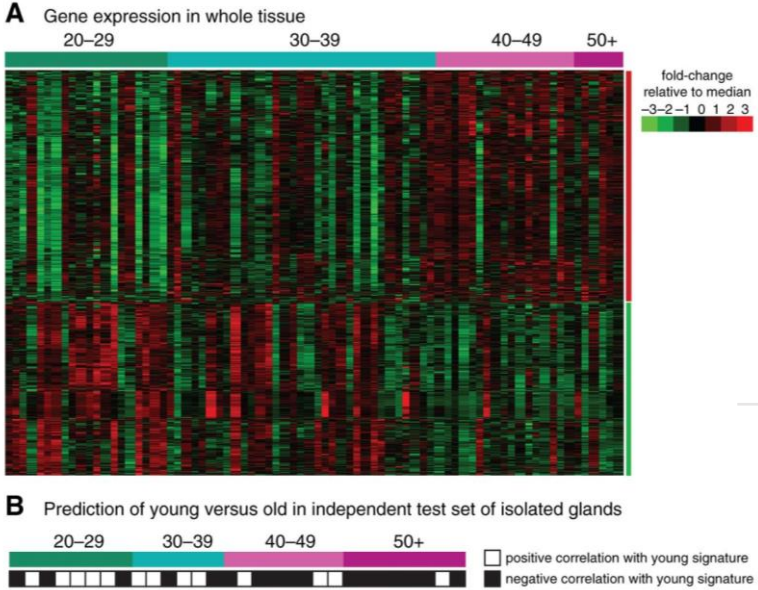
Correlation of gene expression and drug-response data. For each gene and drug combination, the degree of correlation is calculated by multiplying the expression of gene i by the response to drug j for each cell line, and summing across the cell lines. Positive numbers (in red) indicate that greater-than-average expression of the gene generally occurs in cell lines with greater-than-average sensitivity to the drug.

Pinkel, Daniel. "Cancer cells, chemotherapy and gene clusters." *nature genetics* 24.3 (2000): 208-210.

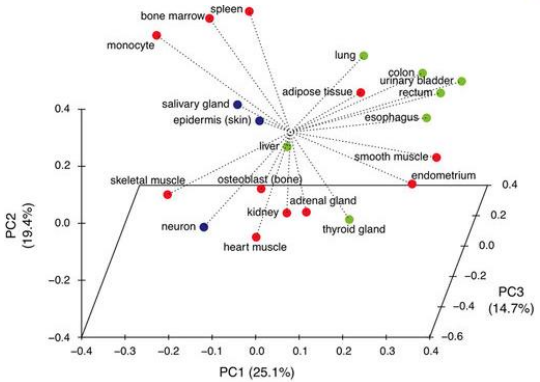
Personalized therapies that combine both therapeutic and computational processes for the effective treatment of senescence-associated conditions:

- Rescue. Get presenescent cells back to healthy state.
- Remove. Eliminate the senescent cells.
- Replenish. Induce regeneration of the cells.
- Reinforce. Prevent the further potential degradation of the tissue/organ.
- Repeat. Apply longevity therapeutics recurrently.

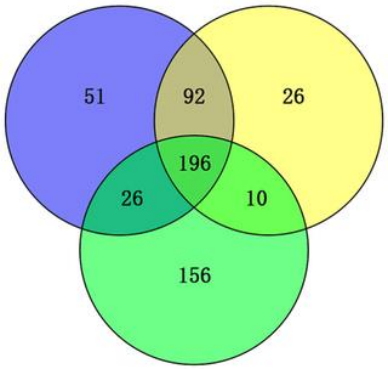
Compare tissue/disease profile to a "young" state



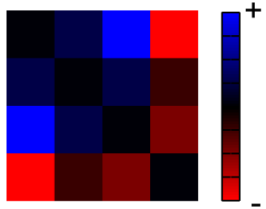
Age-associated gene expression in whole tissue (n = 76) and in isolated glands (n = 30). A, 802 probes were collapsed to unique genes by averaging and a hierarchical cluster analysis (genes-only) shows 2 distinct gene expression groups. Some heterogeneity is observed within groups, but an overall trend is evident. B, the gene expression signature was then used to predict age in an independent test set of isolated glands. Glands from younger patients were more likely to show positive correlation with the young signature from whole glands, whereas older patients were more likely to have negative correlations.



PCA analysis



Venn diagram



Difference matrix

Pirone, Jason R., et al. "Age-associated gene expression in normal breast tissue mirrors qualitative age-at-incidence patterns for breast cancer." *Cancer Epidemiology and Prevention Biomarkers* 21.10 (2012): 1735-1744.

Seim, Inge, Siming Ma, and Vadim N. Gladyshev. "Gene expression signatures of human cell and tissue longevity." *npj Aging and Mechanisms of Disease* 2 (2016): 16014.

IT MAY BE POSSIBLE TO USE THE MOLECULES THAT EXTEND LIFESPAN TO
DEVELOP COMPANION THERAPIES TO INCREASE RESPONSE (E.G. MAJOR NEED IN IMMUNO ONCOLOGY)

IMPORTANT PAPER AND IDEA BY NOVARTIS - 2014

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RESEARCH ARTICLE | IMMUNOLOGY

mTOR inhibition improves immune function in the elderly

Joan B. Mannick[1,*], Giuseppe Del Giudice[2], Maria Lattanzi[2], Nicholas M. Valiante[3], Jens Praestgaard[4], Baisong Huang[1], Michael A. Lonetto[1], Holden T. Maecker[5], John Kovarik[6], Simon Carson[7], David J. Glass[1] and Lloyd B. Klickstein[1]

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[3]Novartis Vaccines and Diagnostics, Cambridge, MA 02139, USA.
[4]Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, USA.
[5]Stanford University School of Medicine, Stanford, CA 94305–5124, USA.
[6]Novartis Pharmaceuticals Corporation, CH-4002 Basel, Switzerland.
[7]Southern Clinical Trials, Christchurch 8024, New Zealand.
↵*Corresponding author. E-mail: joan.mannick@novartis.com
– Hide authors and affiliations

Science Translational Medicine 24 Dec 2014:
Vol. 6, Issue 268, pp. 268ra179
DOI: 10.1126/scitranslmed.3009892

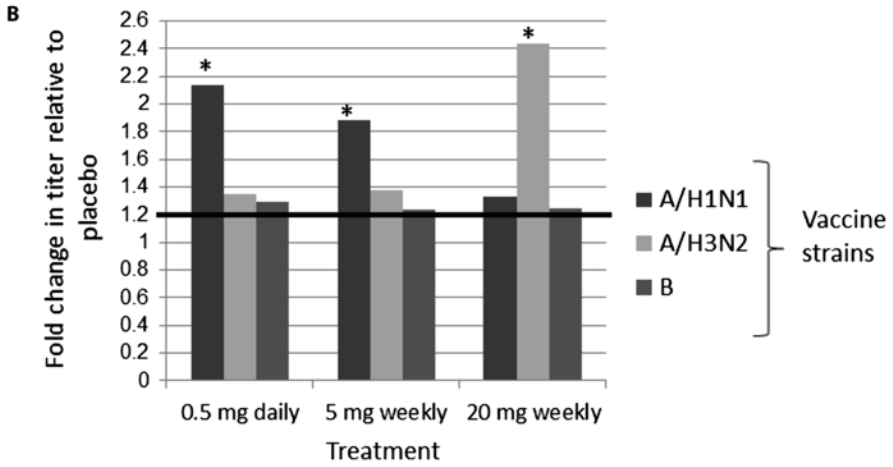


Fig. 1. Increase in antibody titers to influenza vaccine strains in RAD001-treated versus placebo cohorts. (**A**) Increase above baseline in GMTs to each of the three influenza vaccine strains (H1N1 A/California/07/2009, H3N2 A/Victoria/210/2009, and B/Brisbane/60/ 2008) 4 weeks after vaccination in RAD001-treated cohorts relative to the placebo cohort. The fold changes in GMTs relative to the placebo cohort are shown for all of the RAD001 dosing cohorts in the intent-to-treat population. The bold black line indicates the 1.2-fold increase in titers relative to placebo that is required for two of three influenza vaccine strains in order to meet the primary endpoint of the study. Asterisks indicate that the increase in GMT relative to placebo exceeds 1.0 with posterior probability of at least 80%. (**B**) The same data as in (A) are shown for the subset of subjects with baseline influenza titers ≤1:40.

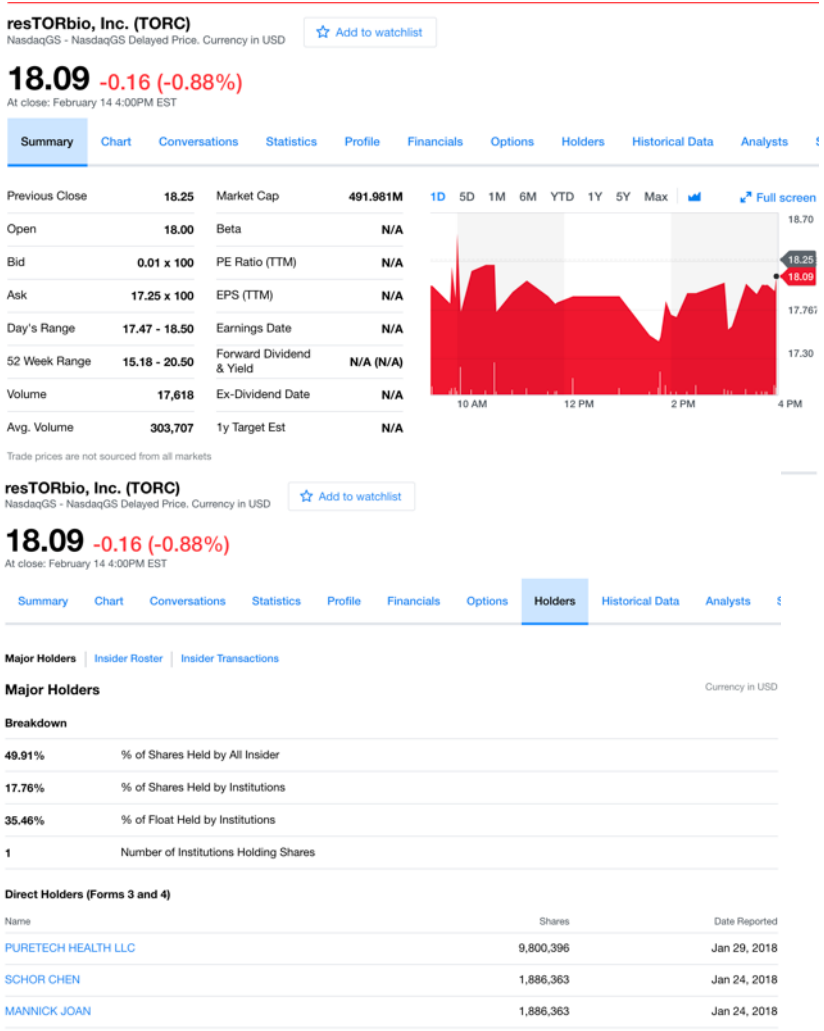
PureTech's resTORbio Licenses Phase II-Stage Novartis Immunosenescence Drugs

PureTech Health is setting up a new subsidiary, resTORbio, to develop two of Novartis's Phase II-stage mechanistic target of rapamycin complex 1 (mTORC1)-targeting drugs as potential therapies for holding back age-related deterioration in immune functioning. Novartis has successfully completed two Phase IIa studies investigating the immune-enhancing potential of mTORC1 inhibitors in elderly patients. resTORbio aims to build on the findings and start Phase IIb studies with the two licensed candidates later this year. The firm said it also plans to extend the program to other age-related disorders.

"mTORC1 inhibitors could lead us to a new paradigm for treating several aging-related conditions," said Chen Schor, a PureTech senior executive who is heading the resTORbio program. "We have a robust clinical development plan for the first indication and plan to explore the program across multiple aging-related diseases."

Novartis will receive an equity stake in resTORbio, plus future milestones and sales royalties, in return for giving the new company an exclusive license to the two mTORC1 programs. "Drug discovery and development is a team sport and we are excited to enter into this agreement with the seasoned leadership at PureTech Health," said Jay Brander, M.D., president of the Novartis Institutes for Biomedical Research (NIBR). "We regard the further development of these compounds by PureTech Health for the potential treatment of conditions such as immunosenescence, as a prime example of our continued commitment to work more openly with innovators beyond our walls to advance projects that have the potential to help patients lead healthier lives."

PureTech says it has set aside about $15 million to invest in tranches in resTORbio, which will give it about a 58% stake in the new operation, although it does have an option to invest another $10 million, which would take its holding in resTORbio to 67%.



resTORbio, Inc. (TORC)
NasdaqGS - NasdaqGS Delayed Price. Currency in USD

Add to watchlist

18.09 -0.16 (-0.88%)
At close: February 14 4:00PM EST

Summary | Chart | Conversations | Statistics | Profile | Financials | Options | Holders | Historical Data | Analysts

Previous Close	18.25	Market Cap	491.981M
Open	18.00	Beta	N/A
Bid	0.01 x 100	PE Ratio (TTM)	N/A
Ask	17.25 x 100	EPS (TTM)	N/A
Day's Range	17.47 - 18.50	Earnings Date	N/A
52 Week Range	15.18 - 20.50	Forward Dividend & Yield	N/A (N/A)
Volume	17,618	Ex-Dividend Date	N/A
Avg. Volume	303,707	1y Target Est	N/A

1D 5D 1M 6M YTD 1Y 5Y Max | Full screen

Trade prices are not sourced from all markets

resTORbio, Inc. (TORC)
NasdaqGS - NasdaqGS Delayed Price. Currency in USD

Add to watchlist

18.09 -0.16 (-0.88%)
At close: February 14 4:00PM EST

Summary | Chart | Conversations | Statistics | Profile | Financials | Options | Holders | Historical Data | Analysts

Major Holders | Insider Roster | Insider Transactions

Major Holders

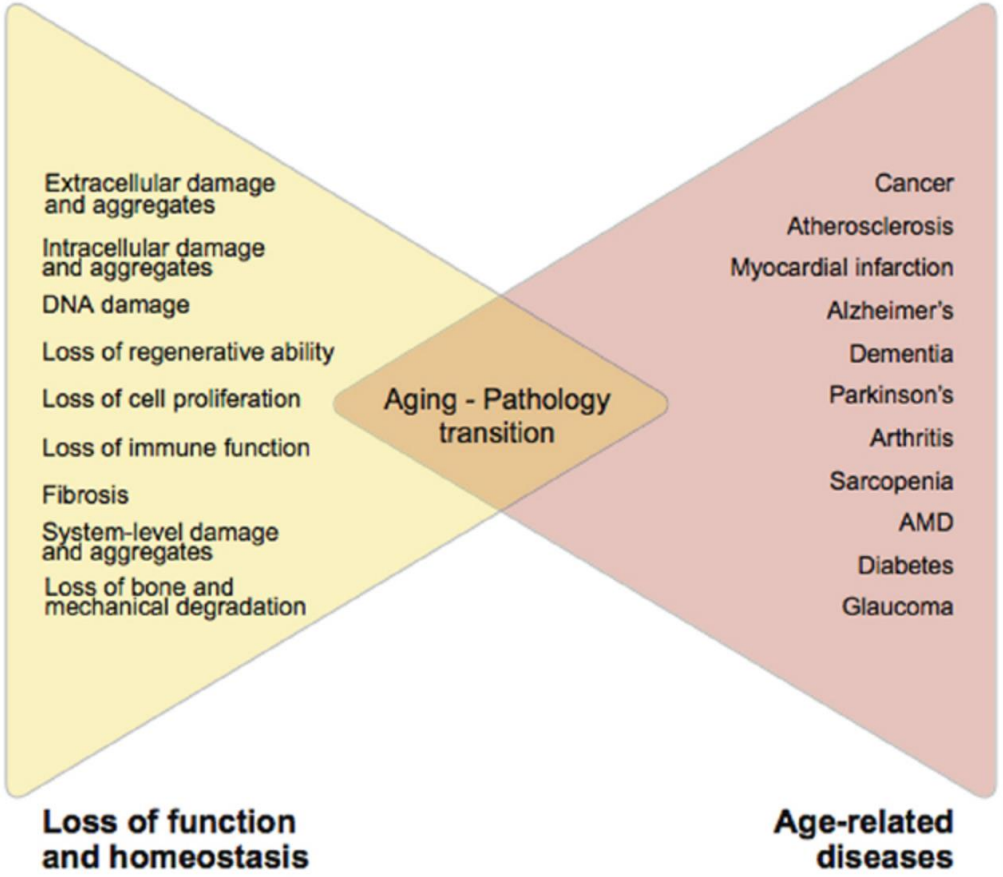
Currency in USD

Breakdown

49.91%	% of Shares Held by All Insider
17.76%	% of Shares Held by Institutions
35.46%	% of Float Held by Institutions
1	Number of Institutions Holding Shares

Direct Holders (Forms 3 and 4)

Name	Shares	Date Reported
PURETECH HEALTH LLC	9,800,396	Jan 29, 2018
SCHOR CHEN	1,886,363	Jan 24, 2018
MANNICK JOAN	1,886,363	Jan 24, 2018



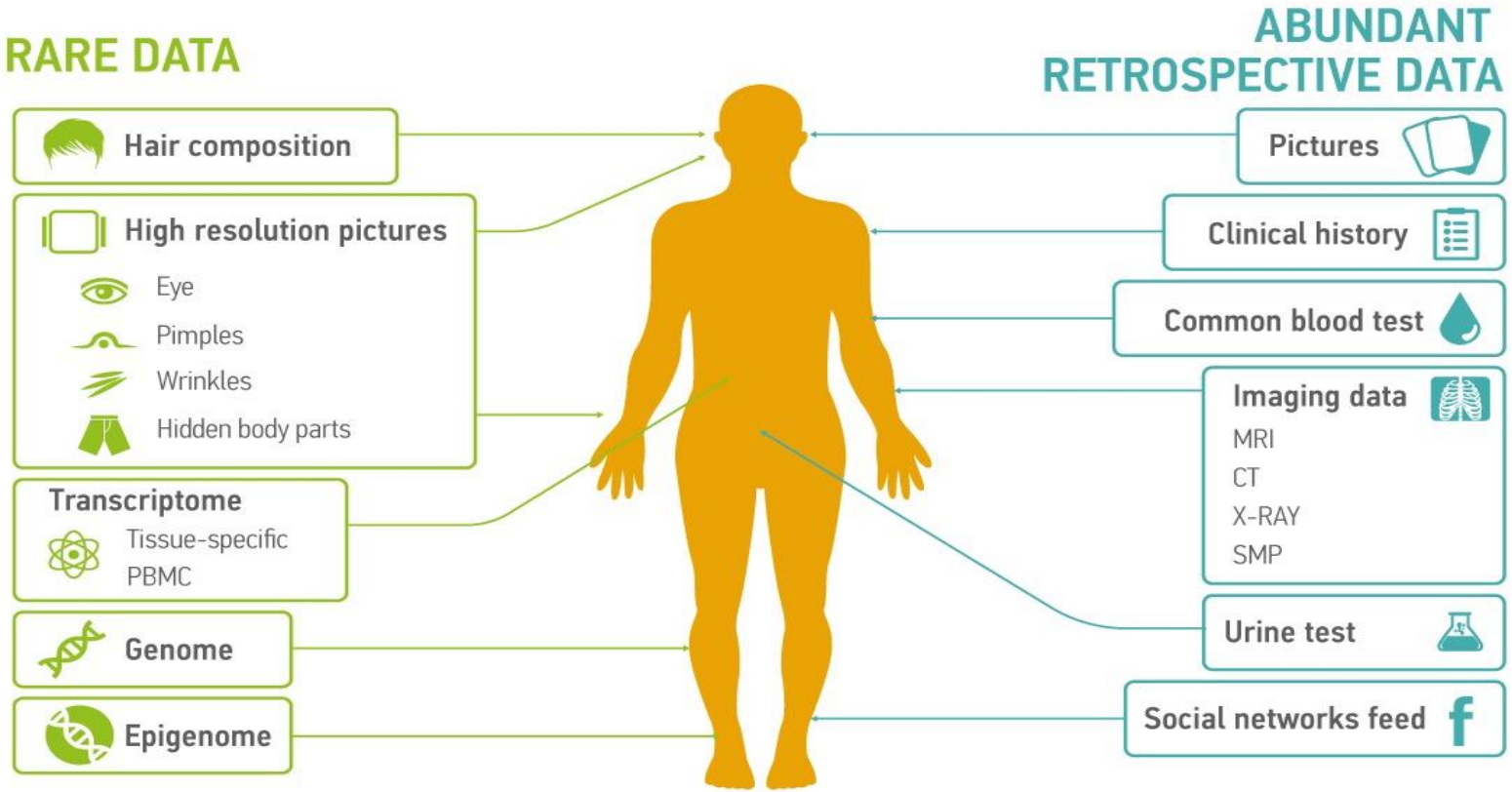
IDEA:

TREAT AGING AS A DISEASE FOR THE PURPOSES OF DL BIOMARKER DEVELOPMENT

TRAIN ON AGE AND RETRAIN ON DISEASES

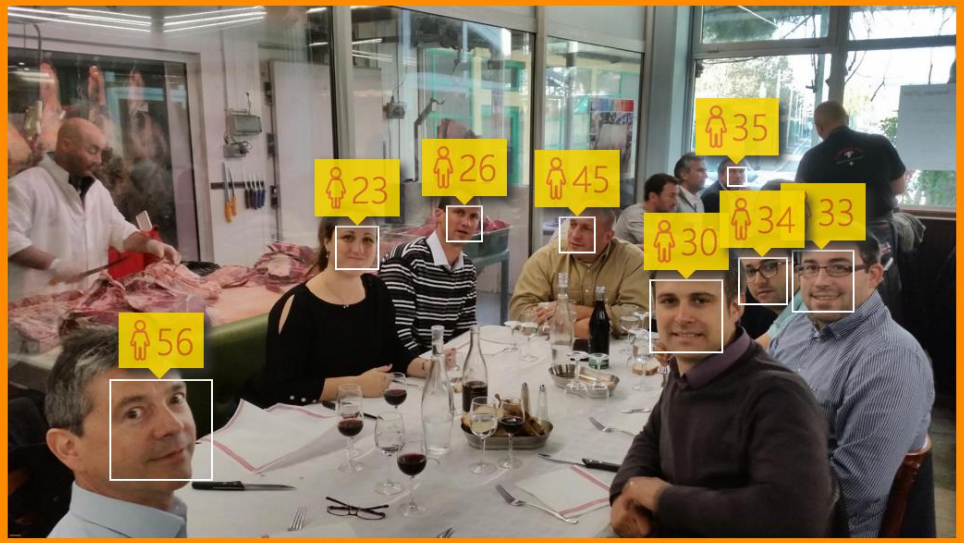
Zhavoronkov A and Bhullar B (2015) Classifying aging as a disease in the context of ICD-11.
Front. Genet. 6:326. doi: 10.3389/fgene.2015.00326

PREDICTIVE DATA TYPES



How-Old.net

How old do I look? #HowOldRobot



Sorry if we didn't quite get it right - we are still improving this feature..

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or

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Microsoft

P.S. We don't keep the photo

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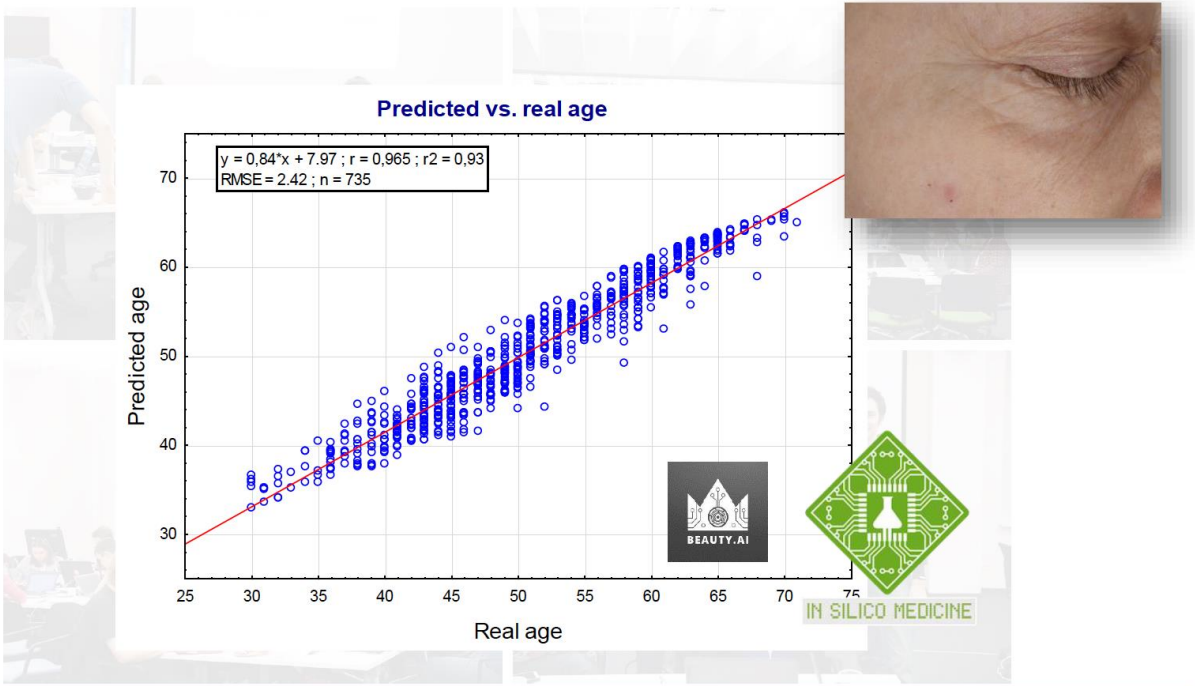
COMPUTER SCIENCE MEETS BIOLOGY AND MEDICINE TO IMPROVE HEALTH AND INCREASE HUMAN LONGEVITY
BY YOUTH LABORATORIES



WELCOME TO AGENET

Contests, hackathons and resources for aging biomarker development. Images, blood tests, tissue samples, clinical parameters, and many other data types will be used in regular competitions. Join the AGENET Facebook Group and use #AGENET and #SKINHACK in social networks when participating in AGENET events.

SKINHACK 1.0 SURPASS MICROSOFT „HOW OLD.NET“





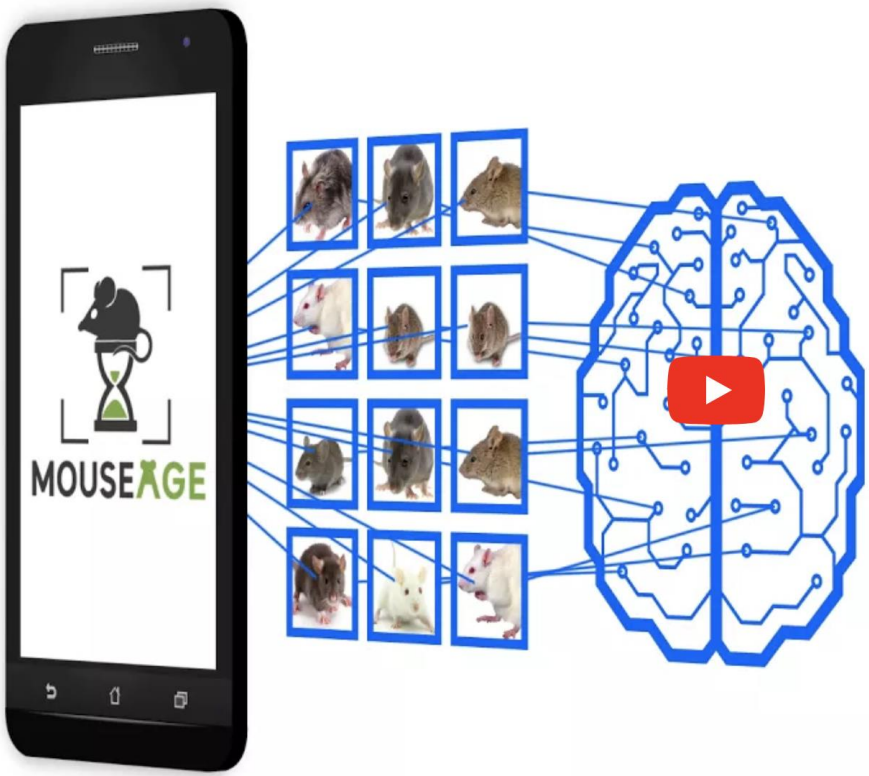
Nastya Georgievskaya

Project lead

Anastasia is the General Manager of Youth Laboratories, a company developing tools to study aging and discover effective anti-aging interventions using advances in machine vision and artificial intelligence. She has a degree in bioengineering and bioinformatics. She won numerous math and bioinformatics competitions and successfully volunteered for some of the most prestigious companies in aging research.

80% of predicted age (evaluation data set) **within ± 2.42 years**

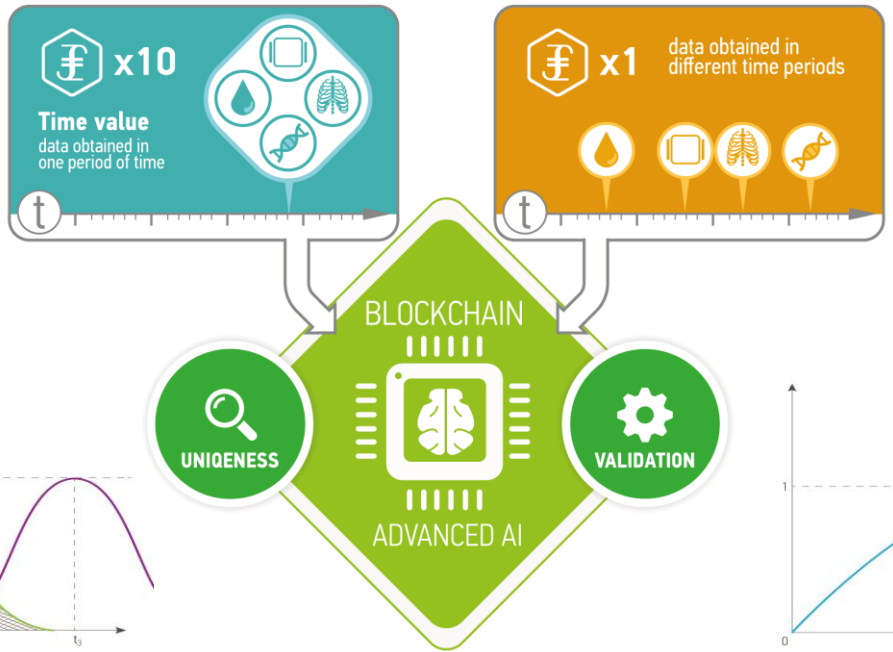
Beiersdorf

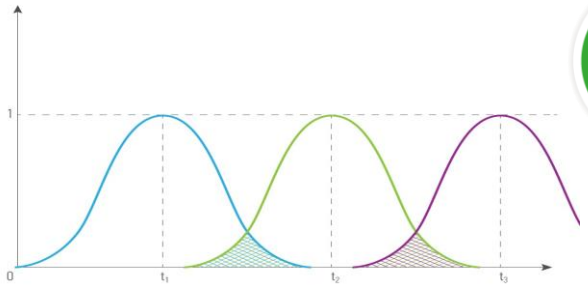




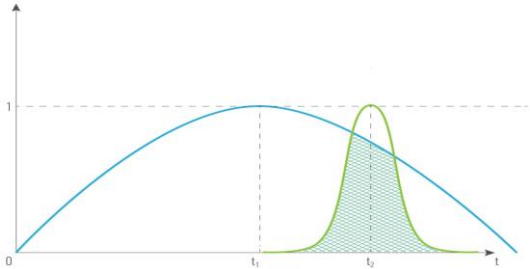
PI: VADIM GLADYSHEV: **vgladyshev@rics.bwh.harvard.edu**

LIFE DATA ECONOMICS ON BLOCKCHAIN: ON THE VALUE OF HUMAN LIFE DATA





Combination value of data of the same type obtained in different periods of time from the single patient



Combination of different data types obtained in different periods of time from the single patient

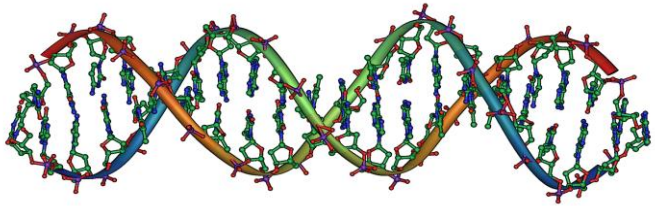
WHAT DATA TYPE IS MORE VALUABLE?

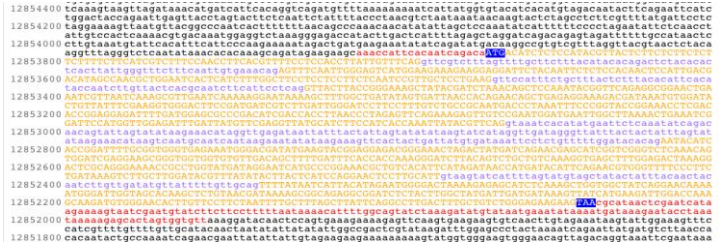
PICTURE



- SEX
- RACE
- EYE COLOR
- HAIR COLOR
- DISEASE PREDISPOSITIONS
- GENETIC DISEASES
- **AGE**
- **WEIGHT**
- **HEIGHT**
- **SKIN HEALTH**
- **SOCIAL STATUS**
- …

GENOME





WHAT DATA TYPE IS MORE VALUABLE?

PICTURE



+

CLINICAL BLOOD TEST

?



MOUSEAGE

Photographic Aging Clock in Mice

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Converging blockchain and next-generation artificial intelligence technologies to decentralize and accelerate biomedical research and healthcare

Polina Mamoshina[1,2], Lucy Ojomoko[1], Yury Yanovich[3], Alex Ostrovski[3], Alex Botezatu[3], Pavel Prikhodko[3], Eugene Izumchenko[4], Alexandr Aliper[1], Konstantin Romantsov[1], Alexander Zhebrak[1], Iraneus Obioma Ogu[5] and Alex Zhavoronkov[1,6]

[1] Pharmaceutical Artificial Intelligence Department, Insilico Medicine, Inc., Emerging Technology Centers, Johns Hopkins University at Eastern, Baltimore, Maryland, USA

[2] Department of Computer Science, University of Oxford, Oxford, United Kingdom

[3] The Bitfury Group, Amsterdam, Netherlands

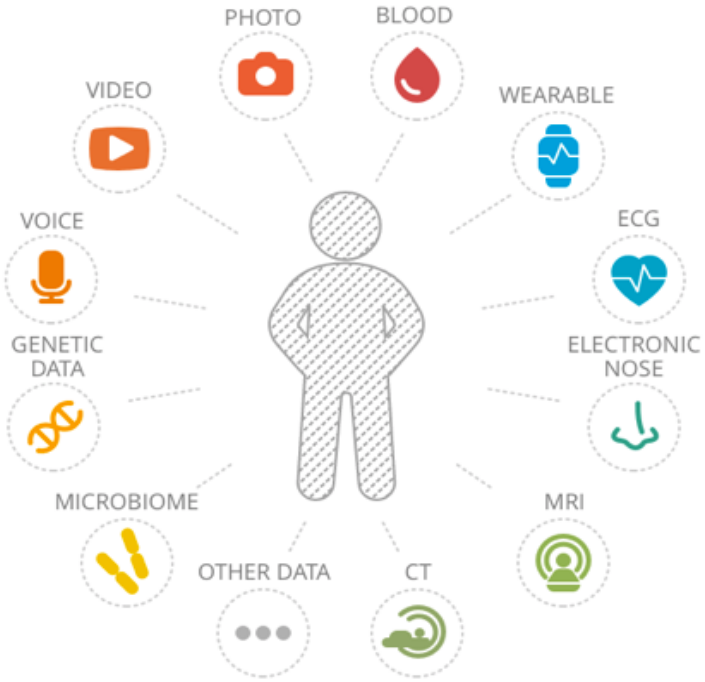
[4] Department of Otolaryngology-Head & Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[5] Africa Blockchain Artificial Intelligence for Healthcare Initiative, Insilico Medicine, Inc, Abuja, Nigeria

[6] The Biogerontology Research Foundation, London, United Kingdom

Correspondence to: *Alex Zhavoronkov,* ***email:*** *alex@insilico.com*

Oncotarget, published on November 9th, announced November 15th link: www.longenesis.com



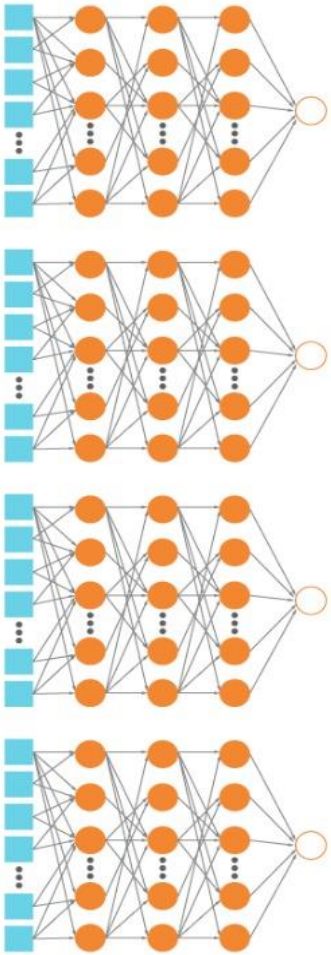
Track your age at every level!



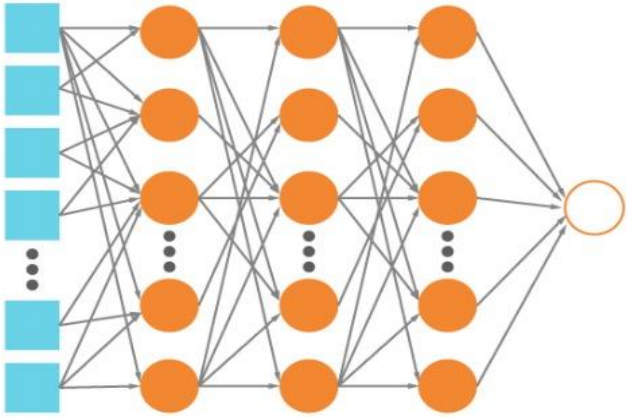
See what makes you younger or older!

BIG IDEA: **USE AGE FOR MULTIOMICS DATA INTEGRATION**

- Features from simple blood tests (biochem)
- Features from simple urine tests (biochem)
- Blood Transcriptome/proteome
- Tissue-specific Transcriptome/proteome
- Urine Transcriptome/proteome
- Genome
- Metabolome
- Imaging data (MRT/CT)
- Pictures
- Hair/Nail/Skin composition



Individual DNNs & Feature Importance Analysis



Multi-modal one-shot learning DNNs & Feature Importance Analysis



alex19
38 years
Weight: 82 lb. Height: 182 in

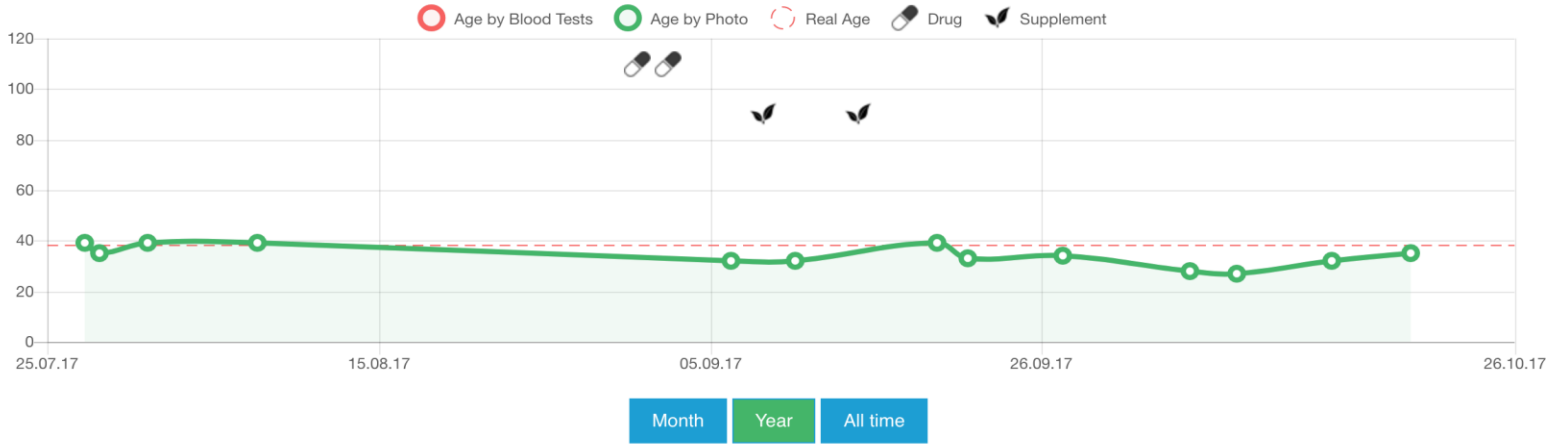
DASHBOARD
Dashboard
Blood Tests
Photo
Additional Tests
Advanced Blood Tests
Basic Urine Test
Transcriptome (blood)
Tissue Transcriptomes
Picture of the Hand
Picture of the Eye
Full Body Picture

Young.AI beta 1.0

Welcome to Young.AI biological age tracker.

Add blood test Add Photo

Track your age, daily activity



Glucose
Please, enter more data

RBC - red blood cells (Erythrocytes)
Please, enter more data

Cholesterol
Please, enter more data

Creatinine
Please, enter more data



alex19
38 years
Weight: 82 lb. Height: 182 in

DASHBOARD
Dashboard
Blood Tests
Photo
Additional Tests
Advanced Blood Tests
Basic Urine Test
Transcriptome (blood)
Tissue Transcriptomes
Picture of the Hand
Picture of the Eye
Full Body Picture

Photos



35 years
2017-10-20



32 years
2017-10-15



27 years
2017-10-09



28 years
2017-10-06



32 years
2017-09-28



36 years
2017-09-28



34 years
2017-09-22



32 years
2017-09-22

www.impactaging.com AGING, May 2016, Vol 8 No 5

Research Paper

Deep biomarkers of human aging: Application of deep neural networks to biomarker development

Evgeny Putin [1,2], Polina Mamoshina[1,3], Alexander Aliper[1], Mikhail Korzinkin[1], Alexey Moskalev[1,4], Alexey Kolosov[5], Alexander Ostrovskiy[5], Charles Cantor[6], Jan Vijg[7], and Alex Zhavoronkov[1,3]

Abstract: One of the major impediments in human aging research is the absence of a comprehensive and actionable set of biomarkers that may be targeted and measured to track the effectiveness of therapeutic interventions. In this study, we designed a modular ensemble of 21 deep neural networks (DNNs) of varying depth, structure and optimization to predict human chronological age using a basic blood test. To train the DNNs, we used over 60,000 samples from common blood biochemistry and cell count tests from routine health exams performed by a single laboratory and linked to chronological age and sex. The best performing DNN in the ensemble demonstrated 81.5 % epsilon-accuracy $r = 0.90$ with $R^2 = 0.80$ and MAE = 6.07 years in predicting chronological age within a 10 year frame, while the entire ensemble achieved 83.5% epsilon-accuracy $r = 0.91$ with $R^2 = 0.82$ and MAE = 5.55 years. The ensemble also identified the 5 most important markers for predicting human chronological age: albumin, glucose, alkaline phosphatase, urea and erythrocytes. To allow for public testing and evaluate real-life performance of the predictor, we developed an online system available at http://www.aging.ai. The ensemble approach may facilitate integration of multi-modal data linked to chronological age and sex that may lead to simple, minimally invasive, and affordable methods of tracking integrated biomarkers of aging in humans and performing cross-species feature importance analysis.

41 parameters
MAE ~5.6 years

Performed permutation feature importance analysis

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Indonesian scientists hamstrung by year-long funding delay

The country's dedicated science fund has failed to raise enough money to finance projects.



Technology Feature | 20 February 2018



Deep learning for biology

A popular artificial-intelligence method provides a powerful tool for surveying and classifying biological data. But for the...

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The limitations of Steven optimism

Ian Goldin questions an oversimp for our complex era.

MENU nature International journal of science

And then there's the challenge of understanding exactly how these algorithms are building the characteristics, or features, that they use to classify data in the first place. Computer scientists are attacking this question by changing or shuffling individual features in a model and then examining how those tweaks change the accuracy of predictions, says Polina Mamoshina, a research scientist at Insilico Medicine in Baltimore, Maryland, which uses deep learning to improve drug discovery. But different neural networks working on the same problem won't approach it in the same way, Greene cautions. Researchers are increasingly focusing on algorithms that make both accurate and explainable predictions, he says, but for now the systems remain black boxes.

Nature **554**, 555-557 (2018)

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 00, No. 00, 1–9
doi:10.1093/gerona/gly005
Advance Access publication XXXX XX, XXXX

OXFORD

Original Article

Population-Specific Biomarkers of Human Aging: A Big Data Study Using South Korean, Canadian, and Eastern European Patient Populations

Polina Mamoshina,[1,2] Kirill Kochetov,[1,3] Evgeny Putin,[1,3] Franco Cortese,[4,5,6] Alexander Aliper,[1] Won-Suk Lee, PhD,[7] Sung-Min Ahn, PhD,[7] Lee Uhn, MD,[7] Neil Skjodt, MD,[8,9] Olga Kovalchuk, MD-PhD,[8,9] Morten Scheibye-Knudsen, MD,[10] and Alex Zhavoronkov, PhD[1,5,*]

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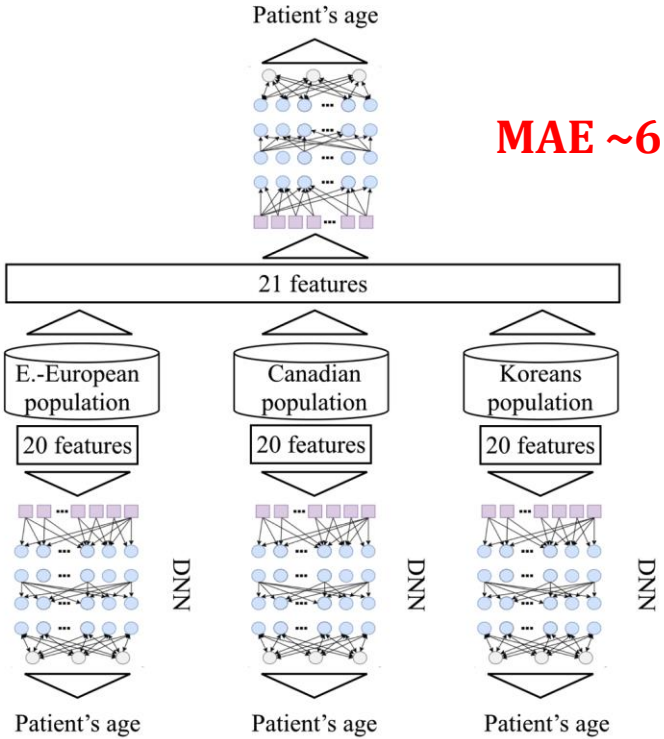
Received: June 5, 2017; Editorial Decision Date: December 27, 2017

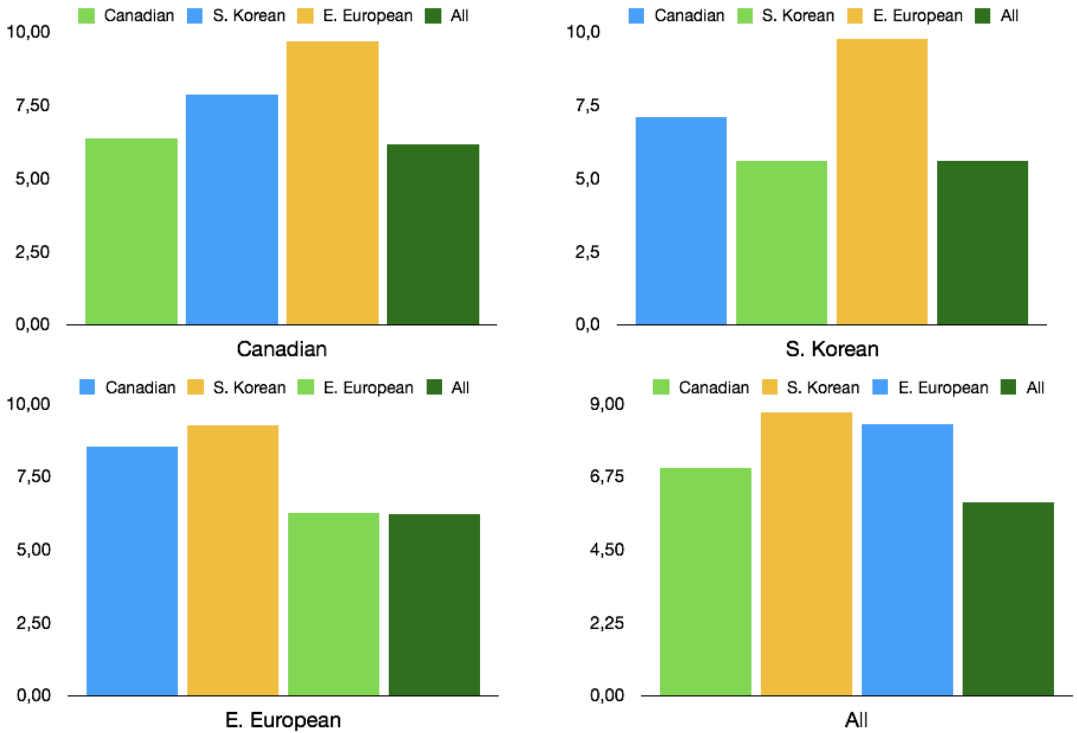
Decision Editor: Rafael de Cabo, PhD

POPULATION-SPECIFIC BIOMARKERS OF HUMAN AGING



MAE ~6 YEARS

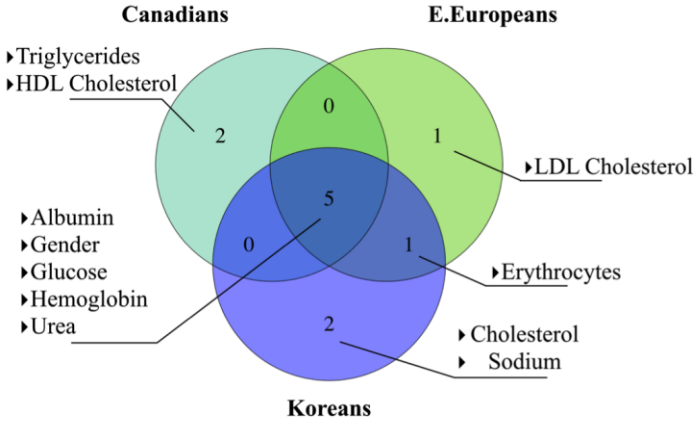
POPULATION SPECIFIC BIOMARKERS OF HUMAN AGING

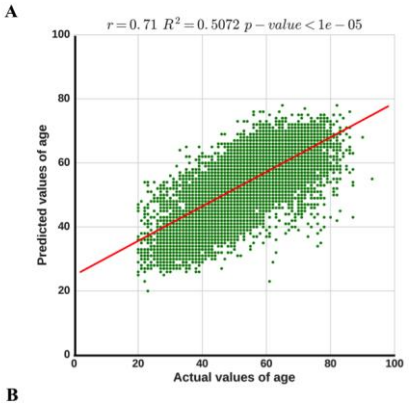


Model trained on the all populations is more accurate in predicting age of samples from individual populations

POPULATION SPECIFIC BIOMARKERS OF HUMAN AGING

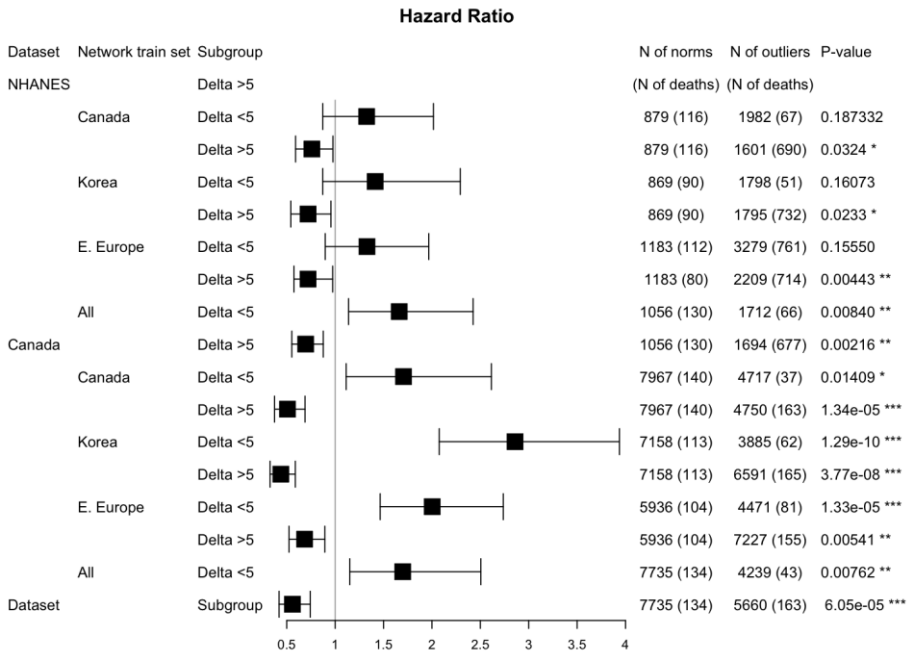
The model trained on 22 parameters achieved:
R^2 of 0.64
MAE of 5.94 years





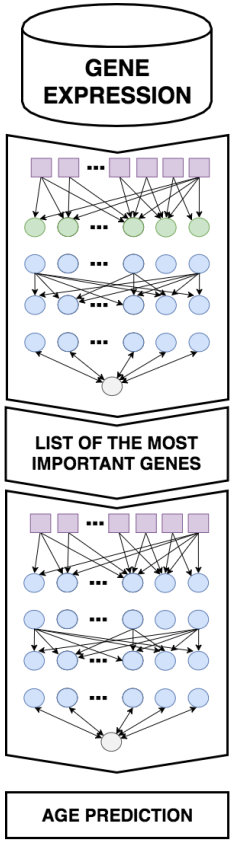
4 the most important parameters for all populations:
Albumin
Glucose
Hemoglobin
Urea

POPULATION SPECIFIC BIOMARKERS OF HUMAN AGING

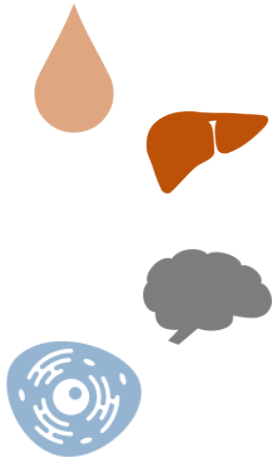


Patients **predicted older** their chronological age have **higher hazard ratio**, while patients predicted **younger** have **lower hazard ratio**.

TRANSCRIPTOMIC TISSUE SPECIFIC BIOMARKERS OF HUMAN AGING



Gene expression of tissue biopsies:
Whole blood
Liver
Brain
Peripheral blood mononuclear cells
Linked to chronological age



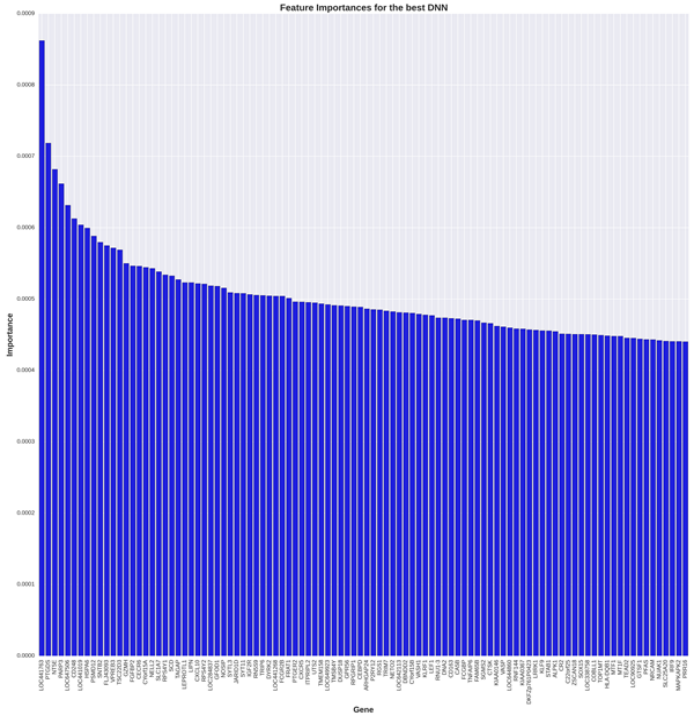
“Cellular lifespan” varies dramatically between different tissues.

Aging clocks should be tissue-specific.

Anti-aging interventions should be tissue-specific.

UNPUBLISHED

LIST OF THE MOST IMPORTANT GENES IN AGE PREDICTION AS POTENTIAL GEROPROTECTOR TARGETS



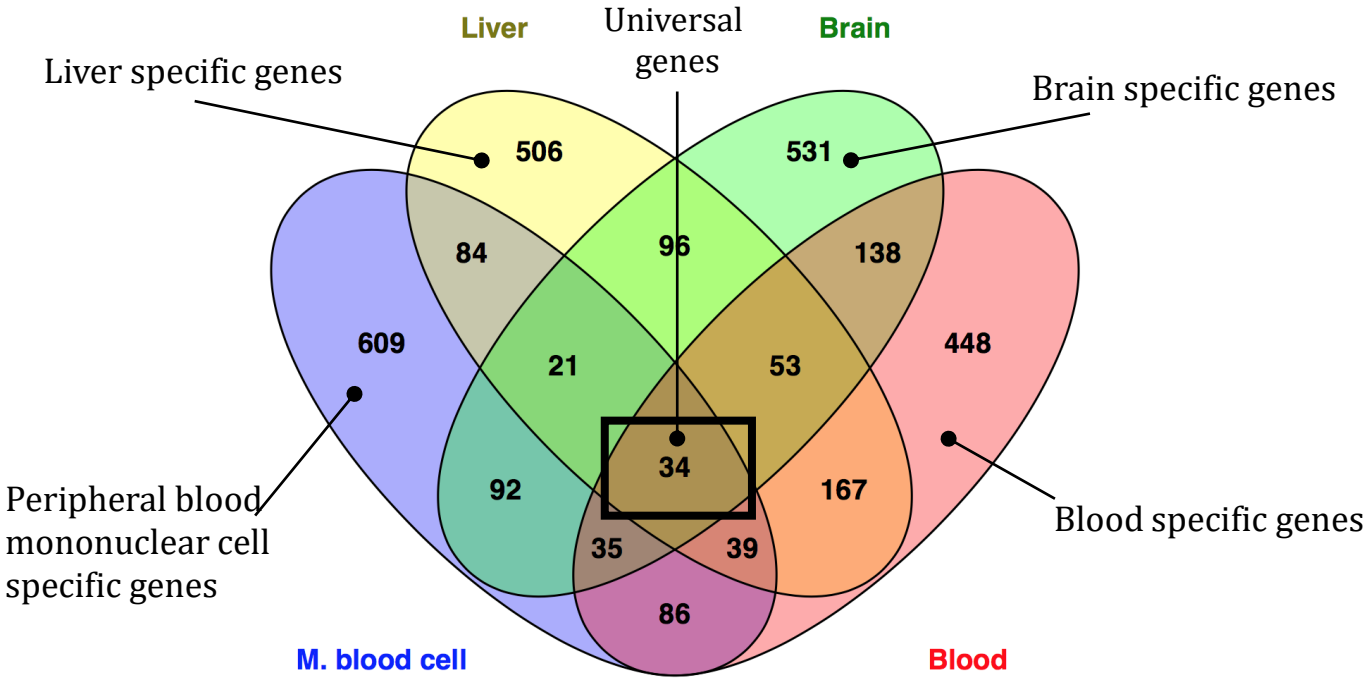
The best model archived:
R^2 of 0.78
MAE of 4.2 years

Top genes are related to
Metabolism and energy homeostasis
Hypertension and hypoxia
Neuropathy
Genomic stability
Smooth muscle contraction
Age-related macular degeneration
Tumor angiogenesis
Inflammation

UNPUBLISHED

Top 100 the most important genes in age prediction from PBMC

SHARED AND UNIQUE THE MOST IMPORTANT GENES IN AGE PREDITION FOR DIFFERENT TISSUES



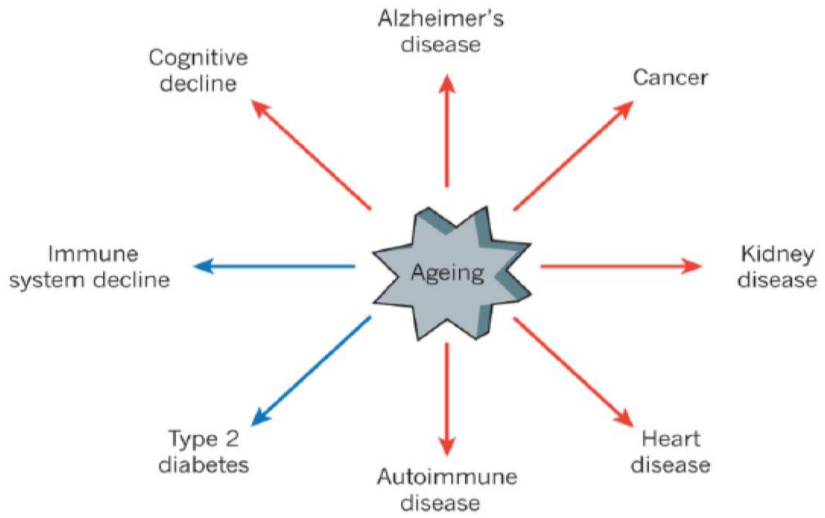
Top 500 the most important genes

UNPUBLISHED

WHY EVERYONE NEEDS DEEP LEARNING FOR AGING BIOMARKERS AND WHY DO WE DO IT?

1. BUILD THE BIOMARKERS OF IMMUNO SENESCENCE
2. PERSONALIZE VACCINES FOR INDIVIDUAL BIOLOGICAL AGE
3. TEST GEROPROTECTIVE MOLECULES AS COMPANION THERAPEUTICS FOR A VARIETY OF VACCINES AND IO
4. UNDERSTAND THE BIOLOGICAL RELEVANCE OF DATA
5. UNDERSTAND THE VALUE OF DATA
6. UNDERSTAND THE POPULATION- AND LIFESTYLE- SPECIFICITY
7. DATA INTEGRATION AND TRANSFER LEARNING

5th ANNUAL AGING RESEARCH FOR DRUG DISCOVERY FORUM
2nd AI & BLOCKCHAIN FOR HEALTHCARE
AT EMBO/BASEL LIFE



Source: Nature 493,17 January 2013

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ARTIFICIAL INTELLIGENCE FOR AGING BIOMARKERS & AGE MANAGEMENT RESEARCH

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