Research Paper

Hallmarks of aging-based dual-purpose disease and age-associated targets predicted using PandaOmics AI-powered discovery engine

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ABSTRACT

Aging biology is a promising and burgeoning research area that can yield dual-purpose pathways and protein targets that may impact multiple diseases, while retarding or possibly even reversing age-associated processes. One widely used approach to classify a multiplicity of mechanisms driving the aging process is the hallmarks of aging. In addition to the classic nine hallmarks of aging, processes such as extracellular matrix stiffness, chronic inflammation and activation of retrotransposons are also often considered, given their strong association with aging. In this study, we used a variety of target identification and prioritization techniques offered by the AI-powered PandaOmics platform, to propose a list of promising novel aging-associated targets that may be used for drug discovery. We also propose a list of more classical targets that may be used for drug repurposing within each hallmark of aging. Most of the top targets generated by this comprehensive analysis play a role in inflammation and extracellular matrix stiffness, highlighting the relevance of these processes as therapeutic targets in aging and age-related diseases. Overall, our study reveals both high confidence and novel targets associated with multiple hallmarks of aging and demonstrates application of the PandaOmics platform to target discovery across multiple disease areas.

INTRODUCTION

Population aging is a key social, economic, and medical challenge on a global scale, which has created a major, growing need to develop interventions that target the aging process. Because age-associated changes in homeostasis are the major risk factors for the most prevalent human diseases (such as neurological, metabolic, fibrotic, and inflammatory conditions), developing interventions that target aging would also impact multiple age-related diseases and result in unprecedented health benefits [1, 2]. Importantly, the stated goal of geroscience is to extend not only lifespan but also health life expectancy, or healthspan [2], enabling wellbeing in older age, the so-called "healthy aging". Research into longevity pharmacology has exploded in recent years with hundreds of compounds now known to extend lifespan in model organisms [3–7].

Major challenges remain, however, in translating these findings into humans, and ultimately extending lifespan and healthspan by targeting aging mechanisms.

Although the underlying molecular mechanisms of aging remain the subject of debate, several key pathways and processes have been associated with aging processes. These have been conceptualized in the hallmarks of aging composed of: Altered intercellular communications, Cellular senescence, Deregulated nutrient signaling, Epigenetic shift, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction, Stem cell exhaustion, Telomere attrition [8]. The hallmarks of aging have been widely used in the field as a starting point for studies, although they are not perfect, and arguably other mechanisms such as extracellular matrix stiffness [9], retrotranspositions [10] and inflammation [11] have also been reported to play an important role in aging. These heterogeneous processes have in turn been associated with age-related diseases. For example, cellular senescence has been associated with pathologies such as cancer, type 2 diabetes, and atherosclerosis [12], as well as pulmonary, neurological, renal, hepatic, infectious, musculoskeletal, and endocrine diseases [13]. At the genetic level, there is a substantial overlap between the genetics of aging and age-associated diseases (AADs) [14]. For example, some known aging-related targets, such as mTOR, AMPK, IGFR, NF-kB, S6K, TGF-β, AT1, Fgf21, FOXO3a, SIRT1, HIF-1, NRF2, and Klotho, may also impact multiple age-associated diseases [1, 8, 15]. Therefore, given that aging is associated with mechanisms that ultimately lead to age-related comorbidities, drugs that act on targets implicated in aging may potentially reduce the severity of gerolavic (from Greek, géros "old man" and epilavís, "harmful") diseases and preventing multimorbidity [16].

A substantial percentage of the human clinical trials, including those evaluating investigational anti-aging drugs, fail in Phase II, a phase where efficacy of the drug is tested [17, 18]. This poor success is in part due to inadequate target choice and the inability to identify a group of patients who will most likely respond to specific agents. This challenge is further complicated by the differences in biological age of the patients, as importance of therapeutic targets varies between the age groups. Hence, identifying potential targets that are implicated in multiple age-associated diseases, and also play a role in the basic biology of aging, may have substantial benefits.

Given the large number of datasets being generated, data-driven approaches (such as artificial intelligence [AI] and machine learning) are becoming instrumental across various fields in biology, including biomarker discovery and target prediction in aging [19]. Indeed, a number of studies by our group and others have employed computational and machine learning analysis to identify new candidates in the context of aging and AADs. These approaches have led to the detection of disease-related genes, caloric restriction genes, and longevity drugs [20–24]. The application of AI in the pharmaceutical industry also aims to reduce the tremendous amount of cost and time conventionally needed to discover new therapeutic targets in various diseases. There are multiple philosophies for the formulation of disease hypothesis, prioritization of pathways implicated in a disease, and selection of promising therapeutic targets. Multiple data types can be used for target discovery including text, imaging, and omics. In recent years, machine learning, and especially deep learning technologies, are rapidly increasing in popularity for target discovery. Advanced signaling pathway modeling such as iPANDA [25] and deep neural networks were used to identify promising protein targets driving complex biological processes implicated in cancer and other diseases [26], drug repurposing [27], and geroprotector discovery [28, 29]. Many of these approaches were implemented in PandaOmics, an industrial target discovery engine. Recently, PandaOmics, has successfully identified and nominated novel targets for idiopathic pulmonary fibrosis (IPF) and kidney fibrosis [30–32].

This platform utilizes advanced deep learning models and AI approaches to predict the target genes associated with a given disease through a combination of Omics AI scores, Text-based AI scores, Finance scores, and Key opinion leader (KOL) scores (Figure 1), and is currently being employed in both academic and industry settings. The algorithm also allows the prioritization of protein targets for novelty, confidence, commercial tractability, druggability, safety, and other key properties that drive target selection decisions. The integrated omics database consists of a vast amount of published systems biology data, spanning over 1,500 diseases and 10,000 disease subtypes. The database includes approximately 1.9 trillion data points derived from over 10 million samples with microarrays, RNA sequencing, proteomes, and methylomes, among other data types. PandaOmics' text database embeds information from over 40 million documents, including patents, grants (that amount to over $2 trillion in funding), publications, clinical trial results, and company reports, among other text-based sources.

In this study, we used PandaOmics to identify a list of potential aging-associated therapeutic targets across various AADs that may be used for drug discovery. We successfully established and validated our unique approach with the application of varied target

identification and prioritization techniques offered by PandaOmics and downstream analyses, yielding a list of dual-purpose targets associated with both the aging process and AADs. First, a list of 145 aging-related targets was generated upon the hallmarks of aging assessment. Subsequently, we further narrowed down the number of potential candidates to a total of 9 highly promising therapeutic targets associated with the aging process and AADs based on multiple selection criteria.

RESULTS

Discovery of targets implicated in multiple age-associated diseases

A combined list of 484 high confidence, 448 medium novel, and 381 highly novel targets were generated from the lists of top-100 targets prioritized by PandaOmics in each of the AADs (Supplementary Figure 1). The top-100 targets for three levels of novelty settings

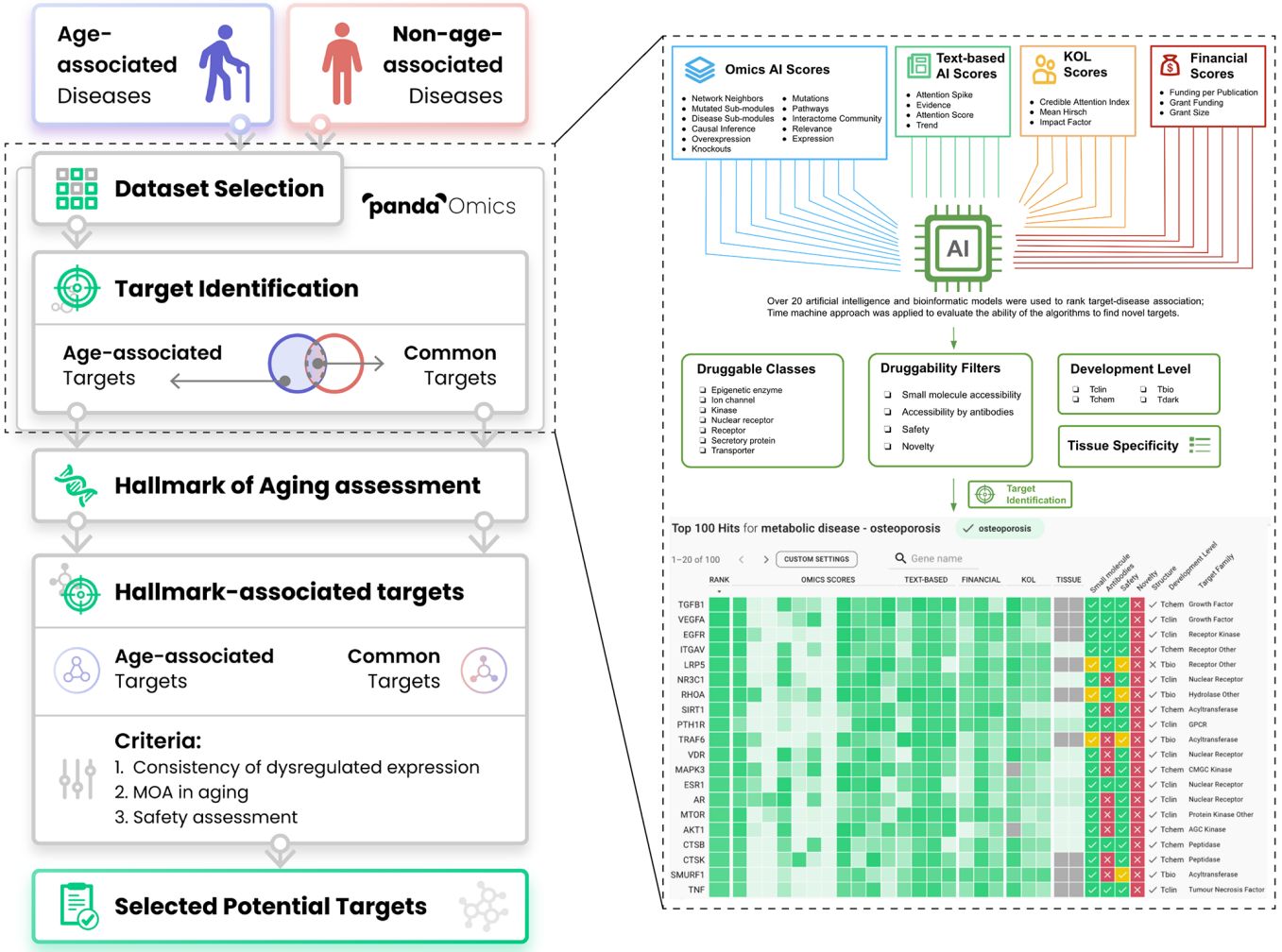

Figure 1. Workflow of the present study. Thirty-three diseases were separated into either age-associated diseases (AADs) or non-age-associated diseases (NAADs) based on the impact of age on the risk of the disease's onset. Their corresponding transcriptomic datasets were retrieved from public repositories and processed by PandaOmics. Age bias between case and control groups has been considered during dataset selection. With multiple levels of novelty settings, targets implicated in AADs and NAADs were identified by 'PandaOmics - target identification'. PandaOmics prioritized targets for one disease and refined the targets based on several flexible druggability filters. The target-disease associations were ranked according to over 20 artificial intelligence and bioinformatics models ranging from Omics AI scores, Text-based AI scores, Finance scores to KOL scores. Target identification was performed independently for each disease. Top-ranked targets shared by both disease categories were regarded as common targets, while targets unique to AADs were defined as age-associated targets (AAD targets). All common targets and AAD targets were subjected to the hallmarks of aging assessment by searching the literature for their evidence in modulating longevity or longevity pathways. To propose potential targets with a dual role in anti-aging and disease treatment, hallmark-associated targets were further evaluated based on their expression profiles across AADs, mechanism of action, and safety. A total of 9 targets were selected, with three levels of novelty. Abbreviation: KOL: Key opinion leader.

Table 1. List of diseases and datasets employed.

Disease	Disease class	Number of comparisons
Age-associated diseases (14 diseases, 87 comparisons)		
Alzheimer's disease	Neurological	12
Amyotrophic lateral sclerosis	Neurological	10
Chronic kidney disease	Metabolic	7
Chronic obstructive pulmonary disease	Inflammatory	6
Cirrhosis of liver	Fibrotic	5
Idiopathic Pulmonary Fibrosis	Fibrotic	11
Obesity	Metabolic	10
Osteoarthritis	Inflammatory	5
Osteoporosis	Metabolic	2
Parkinson's disease	Neurological	4
Primary myelofibrosis	Fibrotic	2
Pulmonary arterial hypertension	Metabolic	5
Rheumatoid Arthritis	Inflammatory	4
Type II diabetes mellitus	Metabolic	4
Non-age-associated diseases (19 diseases, 126 comparisons)		
Acromegaly	Metabolic	2
Asthma	Inflammatory	13
Bipolar disorder	Neurological	4
Celiac disease	Inflammatory	3
Crohn's disease	Inflammatory	8
Cystic fibrosis	Fibrotic	5
Hepatitis, alcoholic	Metabolic	3
Hepatitis C virus infection	Infectious	2
Huntington's disease	Neurological	5
Infectious meningitis	Infectious	3
Influenza	Infectious	5
Multiple sclerosis	Inflammatory	11
Psoriasis	Inflammatory	11
Pulmonary tuberculosis	Infectious	7
Schizophrenia	Neurological	4
Systemic lupus erythematosus	Inflammatory	9
Systemic scleroderma	Fibrotic	6
Type I diabetes mellitus	Metabolic	12
Ulcerative colitis	Inflammatory	13

were selected by (1) the occurrence of the target genes in 14 AADs (Supplementary Figure 2) and (2) the average ranking of the target gene in its corresponding disease (Supplementary Table 1). The same approach was applied to non-age-associated diseases (NAADs). Diseases selected for this study and their corresponding disease classes were listed in Table 1. Only the top-100 genes of this combined list from AADs were subjected to the hallmarks of aging assessment by finding their corresponding evidence in modulating longevity or aging pathways in literature and expression analysis. Under high confidence settings, the top genes identified were *CASP3*, *VEGFA*, and *MMP9*, which were highly ranked in all of the 14 AADs (Figure 2 and Supplementary Figure 2A). *LYN* was the top gene identified under medium novelty settings, which was also highly implicated in all AADs (Supplementary Figures 2B and 3). For high novelty settings, *PPP2CB*, *CDC34*, *FES*, *RHOF*, and *RAB24* were the top-ranked genes in 12 out of 14 AADs (Supplementary Figures 2C and 4). The top-ranked genes shared by both AADs and NAADs were regarded as common targets, while those genes unique to AADs were defined as age-associated targets, or AAD targets (Venn diagram, Figure 1). Intersecting the two

lists of genes obtained from AADs and NAADs resulted in 42 AAD targets in high confidence setting (Supplementary Figure 5A). The remaining 58 genes were considered as common targets. For medium and high novelty settings, 37 and 29 AAD targets were identified, respectively (Supplementary Figure 5B–5C).

Genes implicated in AADs are associated with the hallmarks of aging

In our analysis, 300 genes identified under three different novelty settings were subjected to a literature review (see Materials and Methods) for their association

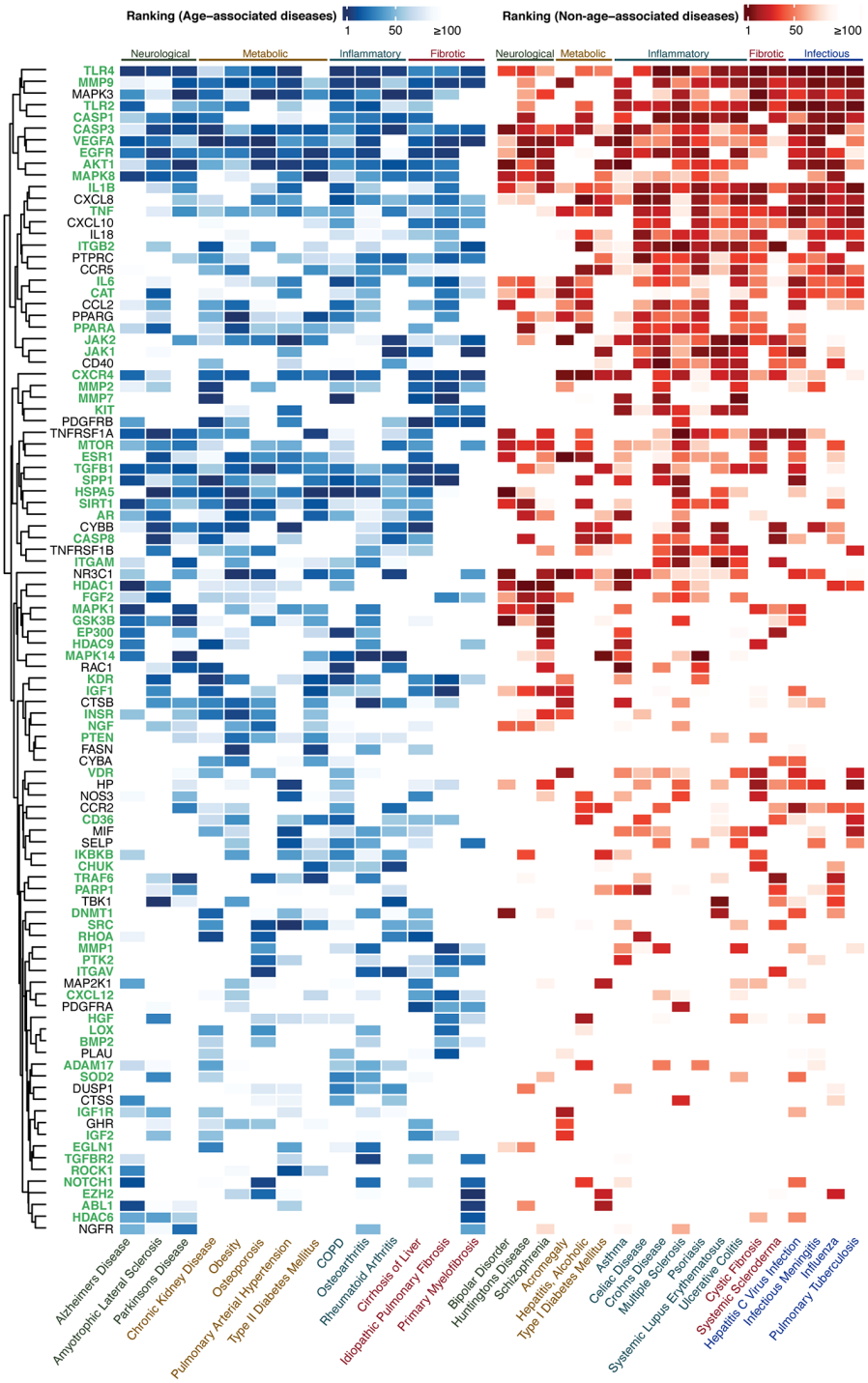

Figure 2. Ranking of the top-100 gene set for AADs under high confidence settings. The ranking of the targets in AADs and NAADs are colored in blue-white and red-white thermal scales respectively. High color intensity stands for high ranking. The lowest ranking was capped at 100. Targets associated with the hallmark(s) of aging are labeled in green. Abbreviation: COPD: Chronic obstructive pulmonary disease.

with the hallmarks of aging. Their corresponding roles in aging processes were summarized in Supplementary Table 2. In total, 145 genes (69 high confidence, 48 medium, and 28 highly novel targets) were linked to at least one aging hallmark (Figure 3, Supplementary Table 2). The most frequently associated aging hallmark was inflammation (n = 48), followed by genomic instability (n = 35), altered intercellular communications (n = 33), mitochondrial dysfunction (n = 32), impaired proteostasis (n = 31) and extracellular matrix stiffness (n = 30). Eighty-six genes (including several well-known aging-associated genes)

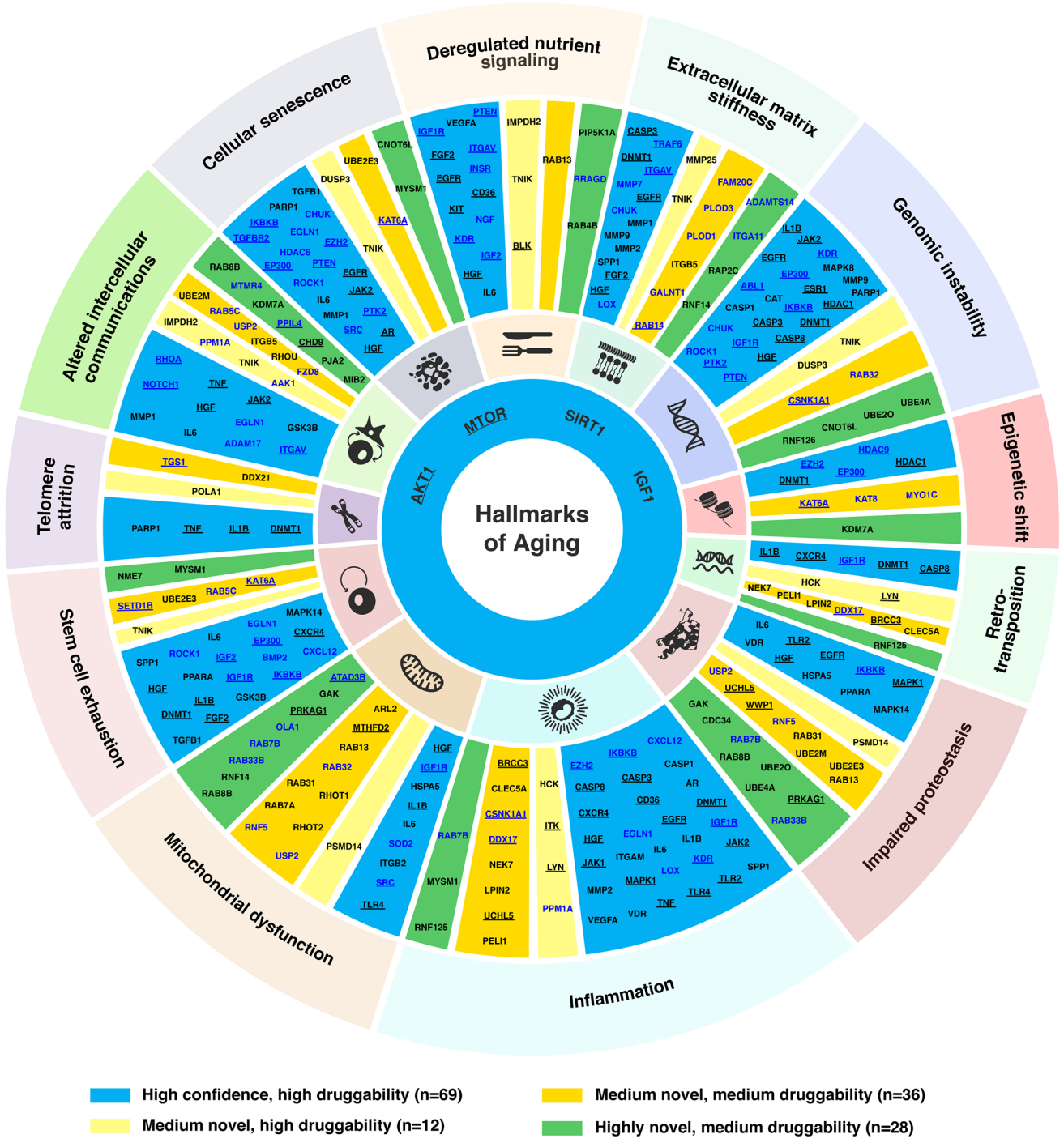

Figure 3. Targets associated with hallmarks of aging. Age-associated targets and common targets (n = 145) were mapped to the corresponding hallmark(s) of aging based on the literature. For novel targets, their participating pathways were also used for the assessment of their association with the hallmark(s) of aging. The four targets connected to all hallmarks (*AKT1*, *MTOR*, *SIRT1* and *IGF1*) are shown in the inner circle of the plot. The target names are labeled in blue for age-associated targets, and black for common targets. Targets annotated as cancer driver genes in the NCG7.0 database are underlined.

were found to be associated with more than one hallmark. In particular, *MTOR*, *SIRT1*, *IGF1*, and *AKT1* were associated with all hallmarks of aging, due to their wide range of interactions with aging-associated pathways. In addition, *IGF1R* was linked to deregulated nutrient signaling, genomic instability, inflammation, mitochondrial dysfunction, retrotranspositions, and stem cell exhaustion. Whereas *HGF* was associated with all hallmarks except epigenetic shift, retrotranspositions, and telomere attrition. Moreover, some novel targets were also identified to be associated with multiple hallmarks of aging. For example, *MYSM1* was associated with cellular senescence, inflammation, and stem cell exhaustion; *KAT6A* was associated with cellular senescence, epigenetic shift, and stem cell exhaustion; *UBE2E3* was linked to cellular senescence, impaired proteostasis, and stem cell exhaustion; *RAB7B* was linked to impaired proteostasis, inflammation, and mitochondrial dysfunction; whereas *RAB8B* and *USP2* were related to altered intercellular communications, impaired proteostasis, and mitochondrial dysfunction. Furthermore, a recently proposed hallmark of aging, extracellular matrix stiffness, was associated with 30 target genes identified by PandaOmics in this study, consisting of 18 high confidence (*AKT1*, *CHUK*, *CASP3*, *DNMT1*, *EGFR*, *FGF2*, *HGF*, *IGF1*, *ITGAV*, *LOX*, *MMP1*, *MMP2*, *MMP7*, *MMP9*, *MTOR*, *SIRT1*, *SPP1*, *TRAF6*), 8 medium novel (*FAM20C*, *GALNT1*, *ITGB5*, *MMP25*, *PLOD1*, *PLOD3*, *RAB14*, *TNIK*), and 4 highly novel targets (*ADAMTS14*, *ITGA11*, *RAP2C*, *RNF14*). Among the 145 genes associated with hallmarks of aging, 55 genes are known cancer drivers (Figure 3) [33], pointing to the aging components underlying cancer pathogenesis.

Genes consistently dysregulated in multiple AADs were implicated as potential dual-purpose targets

To study the dysregulation state of genes identified under three different novelty settings, their consistency of expression change in each AAD class was summarized in Figure 4. Genes that were consistently dysregulated in two or more disease classes in a unidirectional manner were selected for further analysis. For high confidence targets, 52 genes were selected, of which 10 (*CASP3*, *CXCL10*, *CXCL12*, *CYBA*, *HGF*, *ITGAM*, *ITGAV*, *PLAU*, *SPP1,* and *TGFB1*) were consistently upregulated while *MAPK8* was the only gene that was downregulated in all disease classes; 24 genes were upregulated and 8 were downregulated in 3 disease classes. Forty-four medium novel targets were selected, with 4 genes (*CLEC5A*, *FPR3*, *ITGB5,* and *RAB31*) and *PPM1A* being upregulated and downregulated in all disease classes, respectively; 15 genes were upregulated and 10 were downregulated in 3 disease classes. For highly novel targets, 5 of the 45 genes (*MX2*, *P2RX1*, *PRSS23*, *RAB7B,* and *RNASE6*) were upregulated in all classes; 6 genes were upregulated while 21 were downregulated in 3 disease classes. As described above, upon the hallmarks of aging assessment, 145 genes were considered as potential aging-related targets. Here, these genes were further selected with reference to their expression patterns, and a subset of the candidates was considered as potential dual-purpose targets for subsequent analysis (Supplementary Figure 1).

Validation by intersecting the AI-derived targets with well-known aging-associated genes

The significance of the mTOR, the insulin/IGF, and the sirtuin pathways in longevity has been extensively reported, delineating their critical roles in counteracting multiple hallmarks of aging to delay the aging process or to extend lifespan [8, 34, 35]. Remarkedly, Food and Drug Administration (FDA)-approved mTOR inhibitor, rapamycin, was demonstrated to slow down aging and AADs in both preclinical settings and clinical trials [36, 37]. mTOR regulates several hallmarks of aging including nutrient sensing, stem cell exhaustion, proteostasis, and cellular senescence [38]. Upon insulin/IGF receptor activation following the insulin/IGF1 binding, mTOR, a nutrient sensor, regulates cellular functions linked to proliferation, growth, and survival via Akt-mediated activation. Increased insulin sensitivity favored lifespan extension. For example, growth hormone receptor (GHR)-knockout mice showed higher sensitivity to insulin, decelerated senescence, and displayed more phenotypic features related to anti-aging [39]. In addition, activation of SIRT1 suppressed aging by ensuring telomere integrity [40, 41], antagonizing oxidative stress [42, 43], regulating nutrient signaling [8] and maintaining proteostasis [44, 45].

Our approach utilizing PandaOmics identified a set of well-known aging-associated genes that are part of the mTOR, insulin/IGF and sirtuin family signaling (including *IGF1*, *IGF1R*, *AKT1*, *MTOR,* and *SIRT1*), strongly supporting the validity of this promising method for the identification of aging-associated genes. The aging-associated genes listed above were identified as common targets, suggesting their relevance in both aging and other diseases as well as their involvement in multiple signaling networks. It is worth noting that aging genes such as *FOXO* that did not meet the criteria for druggability (see Materials and Methods) were filtered out. To further evaluate whether our approach could identify aging-related targets with potential clinical relevance, the 100 high confidence targets were compared with a pool of well-known aging-associated genes curated from http://ClinicalTrials.gov (focusing on the treatment

of aging), publication, http://Geroprotectors.org [46] (Supplementary Tables 3–5) and aging gene database, GenAge [47]. Fourteen high confidence targets (*ABL1, AR, ESR1, GHR, IGF1, IGF1R, KIT, MAPK14, MTOR, NR3C1, PDGFRB, SIRT1, SRC* and *VDR*) were identified in the pool of 62 genes procured from the aging trials (expected [Exp] = 1.10, fold = 12.70, p = 1.79E-12, Supplementary Table 3). Twenty-

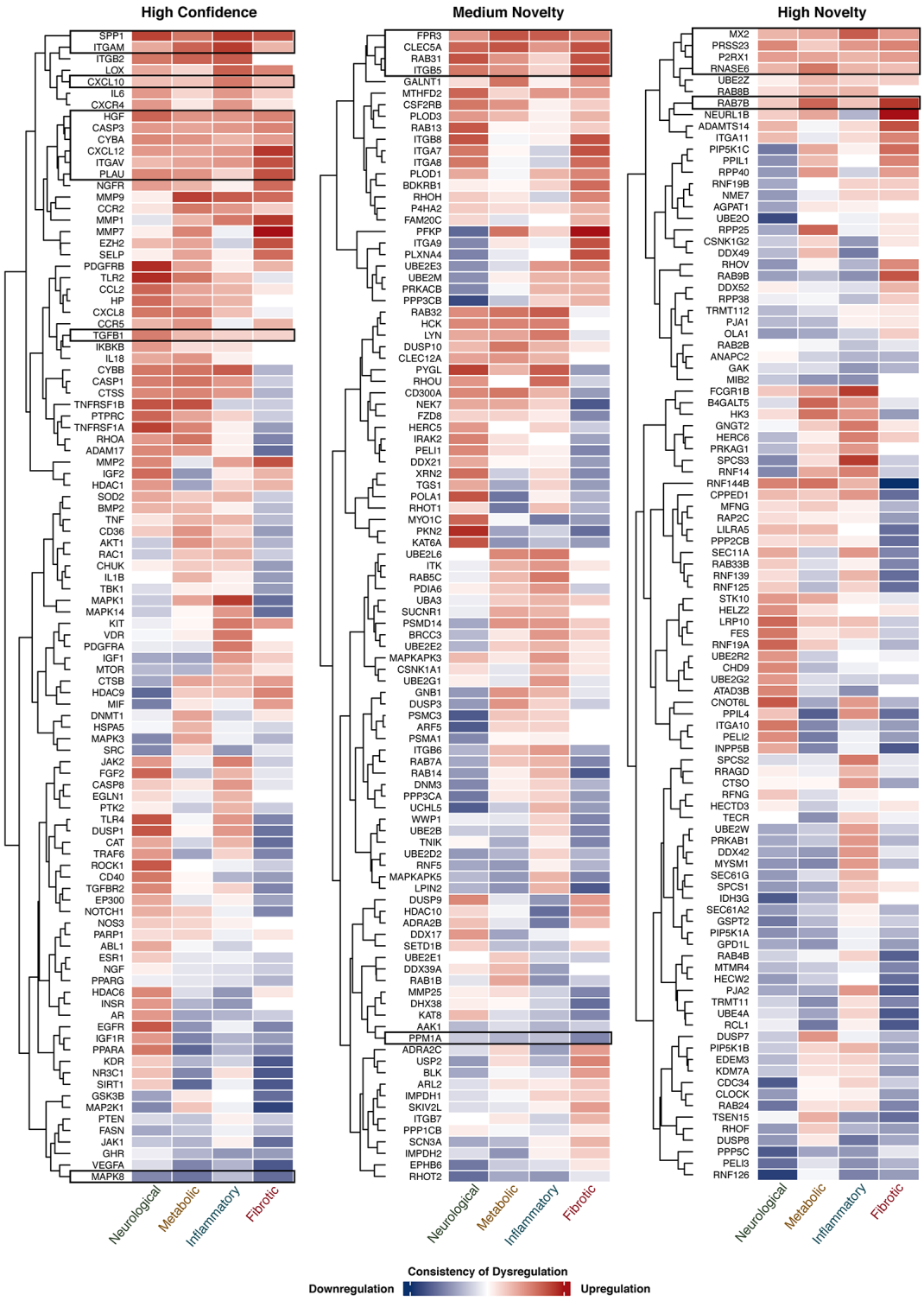

Figure 4. Expression of target genes in 4 AAD classes. The consistency of gene dysregulation in each disease class is indicated by the thermal scale, with red standing for upregulation and blue for downregulation. The color intensity indicates the level of consistency. Target genes consistently dysregulated (≥60% of comparisons) in 4 AAD classes in a unidirectional manner are shown in the black boxes.

four high confidence targets (*AKT1, CASP3, CAT, CHUK, DNMT1, EGFR, HDAC9, IGF1, IGF1R, IL1B, IL6, JAK2, MAPK8, MMP1, MMP2, MMP9, MTOR, PPARA, PTEN, SIRT1, SOD2, TGFB1, TGFBR2* and *TNF)* were identified in the pool of 48 genes procured from publications (Exp = 0.85, fold = 28.13, p = 1.21E-30, Supplementary Table 4). While seven high confidence targets (*CASP1, CASP3, CHUK, ESR1, HSPA5, IKBKB* and *MTOR*) were further identified in the pool of 52 genes procured from geroprotectors (Exp = 0.92, fold = 7.57, p = 3.15E-5, Supplementary Table 5). This significant enrichment might indicate the potential clinical relevance of our AI-derived targets in treating aging-related processes and AADs. Moreover, significant overrepresentation was also observed in 38 high confidence targets that were overlapped with 149 aging-associated genes obtained from the benchmark aging gene database, GenAge (Exp = 2.65, fold = 14.35, p = 1.28E-35), further validating the approach used in this study.

Linking the AI-derived targets to aging-associated pathways by pathway enrichment analysis

Pathway enrichment analysis was performed on 145 AI-derived targets using Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY Database [48]. Genes were mapped to 225 KEGG pathways, of which 151 were significantly enriched (p < 0.05) (Supplementary Table 6) with 110 of the 145 potential targets. PI3K-AKT signaling pathway (hsa04151), MAPK signaling pathway (hsa04010) and FOXO signaling pathway (hsa04068) were in the top 10 enriched signaling axes known to be associated with aging. Notably, the AI-derived targets crosstalk with multiple key aging-associated pathways, such as those regulated by MAPK, PI3K-AKT and FOXO signaling networks (Figure 5), consequently contributing to modulating apoptosis, autophagy, cell proliferation, cell survival, DNA repair, epigenetic alteration, extracellular matrix organization, inflammation,

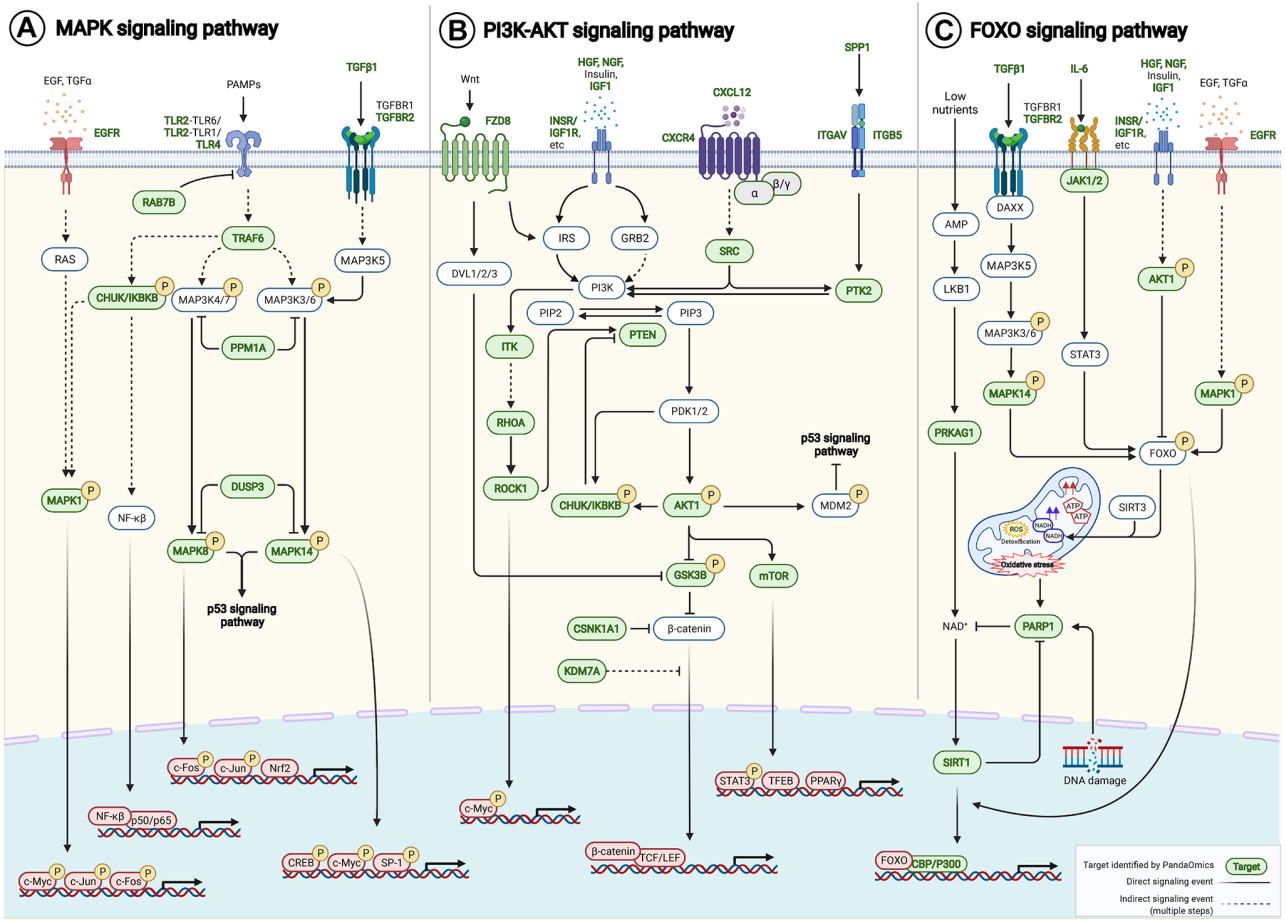

Figure 5. AI-derived targets crosstalk to aging-associated signaling pathways. Pathway enrichment analysis was performed on our 145 AI-derived targets based on KEGG PATHWAY Database. (**A**) MAPK signaling pathway (hsa04010), (**B**) PI3K-AKT signaling pathway (hsa04151) and (**C**) FOXO signaling pathway (hsa04068) were among the top 10 enriched pathways that were known to be associated with aging. Forty-six AI-derived targets were involved. Target-target interactions were identified in the contexts of pathways and networks retrieved from KEGG PATHWAY Database and literature (Supplementary Table 8). Abbreviation: PAMPs: Pathogen-associated molecular patterns.

mitochondrial maintenance, stemness and telomere maintenance (Supplementary Table 2).

AI-derived targets demonstrate dual roles in aging and AADs

The dual-purpose candidates were selected under the considerations of hallmarks of aging assessment (Supplementary Table 2), expression analysis (Figure 4), ranking calculated by PandaOmics, safety assessment, clinical trial status and druggability, yielding a list of 9 potential candidates (Table 2). Selected promising high confidence targets and novel targets are discussed below.

CXCL12

Aging was associated with elevated levels of proinflammatory cytokines, consequently leading to a decrease in mesenchymal stem cell (MSC) ability to regenerate and differentiate in inflammatory conditions [49]. Despite rescuing oxidative stress-induced hematopoietic stem cell (HSC) damage at the mitochondrial level, C-X-C motif chemokine ligand 12 (CXCL12) acted as a proinflammatory cytokine [50]. *CXCL12* was uniformly upregulated in more than 70% comparisons in all four AAD classes i.e., neurological, metabolic, inflammatory, and fibrotic diseases (Figure 6A). In general, the log-fold change (logFC) of *CXCL12* in AADs was significantly higher than in NAADs ($p < 0.001$, Figure 6A). Accumulating evidence demonstrates that CXCL12 upregulation was implicated in AADs including IPF [51], rheumatoid arthritis (RA) [52], and amyotrophic lateral sclerosis (ALS) [53]. Consistent with our findings, upregulation of CXCL12 was suggested to promote migration and proliferation of human lung fibroblast in IPF as well as to enhance monocytes infiltration into the synovial tissue in RA [51, 52]. Treatment with an antagonist of CXCR4, the receptor for CXCL12, extended lifespan, improved motor function, and led to weight loss in ALS *in vivo* [54]. Aging-associated degenerative diseases such as osteoporosis were linked to dysfunctional stem cell differentiation and a decline in the regenerative capacity of musculoskeletal stem cells, resulting from the secretion of pro-inflammatory cytokines such as CXCL12 [49]. Tinzaparin, a CXCL12 inhibitor, is an FDA-approved drug for the treatment of deep vein thrombosis and pulmonary embolism, which are considered as AADs. Taken together, suppression of CXCL12 is one of the potential therapeutic approaches that may be considered towards slowing down aging-associated processes and preventing the onset of AADs.

SPP1

Secreted phosphoprotein 1 (SPP1) functions as Th1 cytokine and is a secreted matrix glycoprotein located in bone and produced by osteoblasts, osteocytes, other hematopoietic cells, or immune cells [55]. *SPP1* was uniformly upregulated in more than 80% comparisons in all four AAD classes, with significantly higher logFC in AADs than in NAADs ($p < 0.001$, Figure 6B). It was suggested that SPP1 may aggravate neurodegenerative, auto-immune, and inflammatory conditions. For example, SPP1 expressed by fast fatigue-resistant or slow motor neurons contributed to the second-wave neurodegeneration in ALS *in vivo* [56]. In addition, elevated levels of SPP1 in cerebrospinal fluid of subjects with Parkinson's disease were associated with more severe motor symptoms. Importantly, *SPP1*-null mice demonstrated reduced neurodegeneration [57]. Besides, SPP1 upregulated lysyl oxidase, an enzyme involved in cross-linking insoluble collagen in fibroblasts. An excess of SPP1 was associated with left-ventricular stiffness and systolic dysfunction in patients with chronic heart failure and hypertensive heart disease [58]. The levels of active TGF-beta and MMP-2, two essential fibrogenic signaling mediators, as well as type I collagen expression were significantly attenuated in *SPP1*-null mice treated with bleomycin, fibrosis inducer, compared to wild-type controls [59]. Taken together, these findings strongly suggest that suppression of SPP1 is a highly potential therapeutic approach for aging and AADs.

ITGB5

Integrin alpha V beta 5 (ITGB5) encodes a subunit of integrin that can interact with several alpha chains to form a variety of integrin heterodimers. *ITGB5* was consistently upregulated in more than 60% comparisons in all four AAD classes, and the logFC of *ITGB5* in AADs was significantly higher than NAADs ($p < 0.05$, Figure 6C). Consistently, *ITGB5* was also found to be upregulated in chronic kidney disease and psoriatic arthritis [60, 61]. In particular, ITGB5 was significantly increased in the serum of patients with psoriatic arthritis, a distinct inflammatory arthritis occurring in 30% of psoriasis patients [60]. ITGB5 was suggested as a biomarker for both nonprogressive and progressive kidney diseases [61], and was also one of the genes strongly associated with ischemic heart disease [62]. Moreover, ITGB5 served as a ligand for Cyr61, a molecule stimulating the production of IL-6, which is considered an aging biomarker, via itgav/itgb5/Akt/NF-κB signaling pathway in RA [63, 64], further supporting its role in various mechanisms underlying multiple AADs.

ADAMTS14

A disintegrin and metalloproteinase with thrombospondin motifs 14 (ADAMTS14) cleaves the amino-propeptides

Table 2. List of prioritized targets.

Target[1]	Protein family	Hallmarks of aging	Dysregulation in AAD classes	Role in aging	Drugs in clinical trials	Severe toxicity[3]	Reference
High confidence							
CXCL12	Cytokine	Inflammation, Stem cell exhaustion	**ALL** Upregulated	CXCL12 is an aging-upregulated gene and a mediator of the crosstalk between vascular cells and many brain cell types (pro-aging; therapy approach: antagonist)	Tinzaparin (phase 4)	No evidence	[94]
SPP1	Chemokine	Extracellular matrix stiffness, Inflammation, Stem cell exhaustion	**ALL** Upregulated	Age-dependent increase in SPP1 levels inhibited skeletal muscle regeneration (pro-aging; therapy approach: antagonist)	ASK-8007 (phase 1/2)	No evidence	[95, 96] NCT00411424
Medium novel							
ITGB5	Receptor	Altered intercellular communications, Extracellular matrix stiffness	**ALL** Upregulated	ITGB5 is a TGF-β activator. TGF-β signaling, being downstream of other signals, was shown to repress body size as well as lifespan *in vivo* (pro-aging; therapy approach: antagonist)	Cilengitide (phase 3)	No evidence	[97] NCT00689221
PPM1A	Esterase	Deregulated nutrient signaling, Inflammation	**ALL** Downregulated	PPM1A stimulated macrophages to produce TNF through TLR4 (anti-aging; therapy approach: agonist)	No	No evidence; absence in DEG	[98]
Highly novel							
RAB7B	Hydrolase	Impaired proteostasis, Inflammation, Mitochondrial dysfunction	**ALL** Upregulated	RAB7B negatively regulated TLR4 signaling in macrophages and autophagic flux as well as prevented inflammation and autophagy upon damage (anti-aging[2]; therapy approach: agonist)	No	No evidence; absence in DEG	[99]
ADAMTS 14	Peptidase	Extracellular matrix stiffness	Upregulated in neurological and fibrotic diseases	ADAMTS14 is responsible for the degradation of ECM collagen. During aging, fibroblast-ECM interactions become disrupted due to the fragmentation of collagen fibrils. Fibroblasts synthesized fewer ECM proteins and more matrix-degrading metalloproteinases (pro-aging; therapy approach: antagonist)	No	No evidence, absence in DEG	[100]
KDM7A	Oxidoreductase	Altered intercellular communications, Genome instability	Downregulated in neurological and fibrotic diseases	Age-related neural dedifferentiation might contribute to many cognitive abilities decline with age. KDM7A regulated neural differentiation through FGF4, and was associated with Wnt signaling (anti-aging; therapy approach: agonist)	No	No evidence	[101, 102]
MYSM1	Peptidase	Cellular senescence, Inflammation, Stem cell exhaustion	Downregulated in neurological, fibrotic and metabolic diseases	MYSM1 functionally reduced cellular senescence and the aging process. MYSM1 deficiency promoted the aging process and decreased lifespan while its overexpression inhibited the aging process and increased lifespan *in vivo*. (anti-aging; therapy approach: agonist)	No	No evidence	[103]
MTMR4	Esterase	Altered intercellular communications	Downregulated in neurological, fibrotic and metabolic diseases	Skeletal muscle atrophy accompanies many chronic disease states and normal aging (anti-aging; therapy approach: agonist)	No	No evidence	[104]

Note: [1]Targets selected for comprehensive target review are in **BOLD**. [2]Based on its mechanism of action i.e., protective role. [3]Database of Essential Gene (DEG) is freely accessible from the website http://tubic.tju.edu.cn/deg.

of fibrillar collagens, enabling collagen fibril formation prior to assembly of collagen, a major extracellular matrix (ECM) protein. *ADAMTS14 was* uniformly upregulated in more than 65% comparisons in neurological and fibrotic diseases. The logFC of *ADAMTS14* in AADs was also significantly higher than in NAADs ($p < 0.01$, Figure 6D). Significant upregulation of ADAMTS14 was observed in human osteoarthritis (OA) cartilage, suggesting its involvement in cartilage matrix anabolism [65]. ADAMTS14 was also linked to the susceptibility to aging-related Alzheimer's disease as well as the regulation of immune functions via TGF-beta signaling [66]. *ADAMTS14*-deficient mice remained healthy, fertile, and displayed normal amino-procollagen processing [67], suggesting that antagonizing ADAMTS14 is unlikely to result in severe toxicity. As such, pharmaceutical inhibition of ADAMTS14 may provide a promising therapeutic approach for aging and AADs.

DISCUSSION

In recent years, extensive efforts have been applied to generating a wide range of transcriptomic, genomic, proteomic, imaging, methylation, and metagenomic aging-related data. However, analysis of such a massive

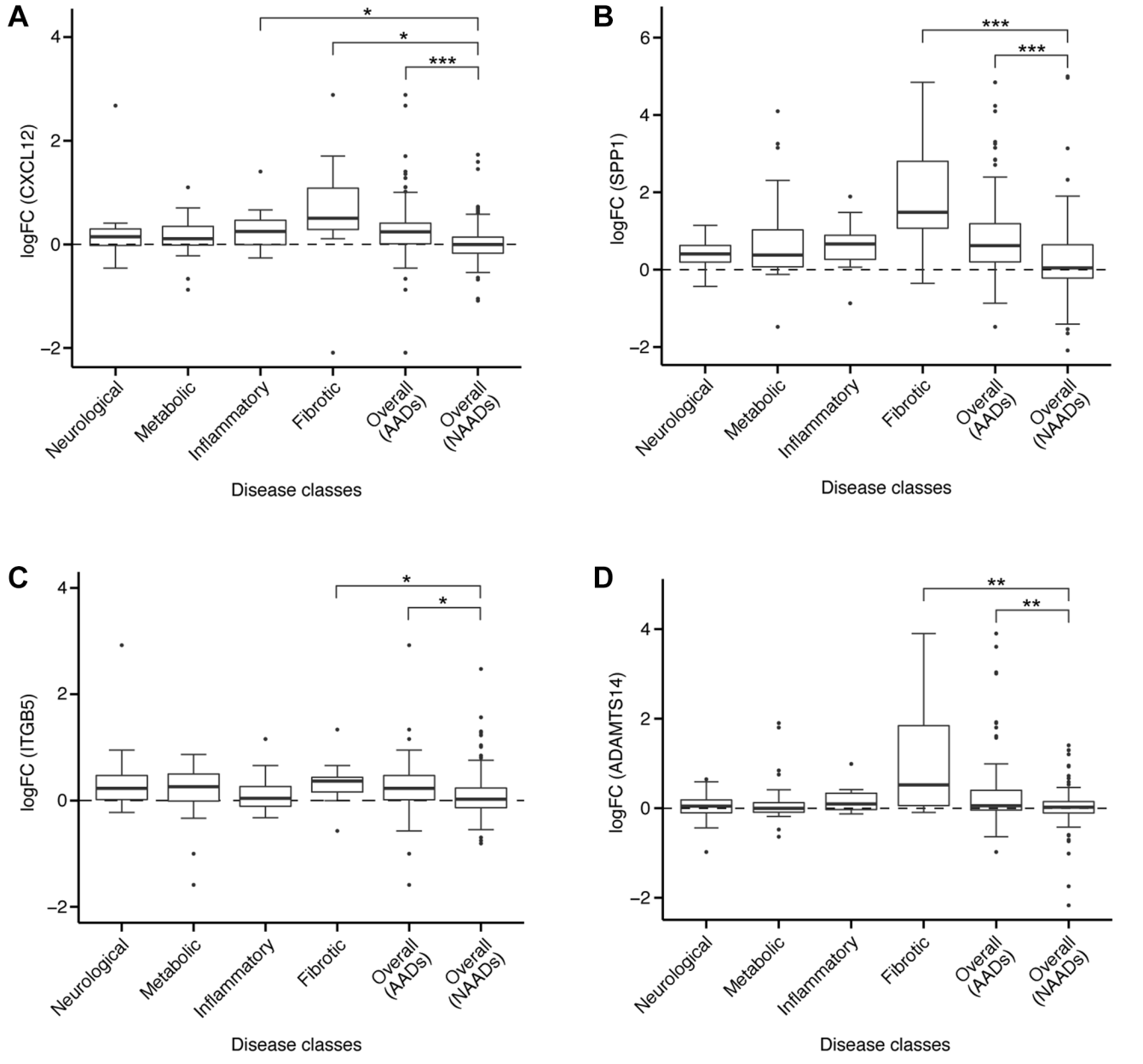

Figure 6. Expression of target genes in different diseases. The logFC of gene expression were shown for (**A**) *CXCL12*, (**B**) *SPP1*, (**C**) *ITGB5*, or (**D**) *ADAMTS14* in AADs and NAADs. For each gene, comparisons of the logFC value were conducted between NAAD and each of the AAD classes, with significant difference indicated by asterisks (two-tailed *t*-test, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

amount of data requires tailored computational approaches, capable of providing a detailed overview of the aging process as well as identifying promising targets for delaying aging and treating age-associated diseases. PandaOmics has several unique advantages with respect to user experience, integrated deep learning-based algorithms, the comprehensive database, and the time machine validation approach [19]. In contrast to other alternatives, PandaOmics platform consists of a diverse set of validated AI analytical models (such as text mining, entity recognition, target ranking, and trend prediction), coupled with the ability to discover novel targets automatically, making this platform unique in the community.

While we acknowledge that inclusion and exclusion of AADs can impact the outcome of our analyses, unfortunately, we could not include all AADs into our study due to limited publicly available datasets for some diseases. Given this limitation, the selection of 14 AADs was based on the consideration of whether age is a strong risk factor for the disease's onset, as well as the availability of public datasets. Cardiovascular diseases were not included in this study due to their common mechanistic root contributing to the insufficient blood supply to multiple organs [68, 69]. Cancers were also excluded, as some of the pathways and mechanisms implicated in tumorigenesis are contradictory to those typically implicated in aging, such as increased cell proliferation [70]. Regarding target selection, some of the aging-associated genes were filtered out due to target family consideration, for example, transcription factors and generic proteins were not included. Furthermore, the current analysis only retrieved transcriptomics data, which, in turn, restricted the depth of analysis. The incorporation of genomic data could bring deeper insights into the shared genetics between aging and aging-associated disorders. Moreover, as aimed to identify dual-purpose targets across aging and multiple AADs, genes that did not meet the dual-purpose were not selected by this approach. It is also worthy to note the trade-off between target novelty and the evidence connecting a target to a disease. The degree of novelty is defined by the volume of related publications, and thus increasing the novelty level will sacrifice the evidence supporting the target's participation in the disease. Therefore, some of the highly novel targets selected by PandaOmics, were not mapped to any aging hallmarks due to the lack of literature support. Nevertheless, they could be potential aging-related target candidates worthy of further investigation.

By combining genes derived from a variety of AADs, we were able to establish potential targets at different levels of novelty. The subsequent association of these targets with pathways known to be involved in aging such as *MTOR*, *SIRT1*, *IGF1*, and *AKT1*. Interestingly, the well-known aging-related genes were often the top-ranked targets in both AADs and NAADs, possibly due to their involvement in a wide spectrum of pathways. Among high confidence targets with the most associated hallmarks were *IGF1R*, *HGF*, *IL6*, *MMP1*, *PARP1*, *SPP1,* and *ROCK1*. Whereas in terms of novel targets, we found *MYSM1*, *KAT6A, UBE2E3*, *RAB7B*, *RAB8B,* and *USP2.* The most frequently associated hallmark of our targets is inflammation. Each proposed target is associated with distinct patterns of aging hallmarks, suggesting complex mechanisms underlying the aging process. Nonetheless, targets associated with multiple hallmarks of aging should be considered for further studies. Notably, while some of the targets revealed by our analysis (such as *IGF1R, HGF, and KAT6A*), are well-characterized drivers of tumorigenesis, others are known tumor suppressors e.g., *PTEN*, *EP300*. While these targets may have a theoretic therapeutic potential in AADs setting, modulating these molecules may elevate the risk of cancer development, and they should be excluded from further consideration.

By further evaluating targets linked to the aging hallmarks and expression changes in AADs, 9 potential candidates were revealed. Many of these targets play roles in inflammation, which is in line with the view that inflammation is associated with multiple age-related diseases and is an intrinsic and major component of the aging processes [71]. As previous studies have also reported strong overlaps of inflammation-related genes between aging and age-related diseases [14], targeting the immune dysfunction in aging could be a powerful approach for improving healthspan [72]. In addition, several strong candidate targets play roles in ECM remodeling. While this signaling network is not a hallmark of aging, it clearly plays an important role during aging [73]. As such, our findings support the view that ECM can be considered as a hallmark of aging and a promising therapeutic target for developing interventions [9].

Considering the potential targets we selected in the present study, the clinical relevance of CXCL12, SPP1, ITGB5 and ADAMTS14 in neurodegenerative, auto-immune, and inflammatory conditions was demonstrated in AADs. Thus, targeting these genes may have major health and clinical benefits for both aging and AADs. Stromal aging fibroblasts expressed and secreted a higher level of CXCL12 than the young cell [74]. In addition, CXCL12 demonstrated an activating role on mature osteoclast by promoting bone-resorbing activity [75], supporting the observation that CXCL12 plasma level was inversely correlated with bone mineral density [76]. Consistently, with age, the rate of bone

resorption exceeded that of bone formation, leading to bone loss. SPP1 modulated osteoclast differentiation [77], and its levels in the plasma of aged human donors were significantly higher than in young individuals, both in a normal state or upon muscle injury [78]. SPP1 was demonstrated to attenuate the regenerative responses of old muscle stem cells. Neutralization of SPP1 recovered and enhanced the myogenic responses of old muscle stem cells, but failed to induce significant effect in young muscle stem cells, revealing the inhibitory effects of the age-dependent increase in SPP1 level on skeletal muscle regeneration [79]. Besides the age-dependent inflammation and bone loss, with age, collagen fibers became fragmented and stiff [73], disrupting various aspects of homeostasis and affecting healthy function. For example, aged fibroblast-ECM interactions were disrupted due to the fragmentation of collagen fibrils. Such fibroblasts synthesized fewer ECM proteins and more matrix-degrading metalloproteinases [80]. ADAMTS14 participates in degradation of ECM collagen. Aging-related increase in ECM stiffness leads to an imbalance in matrix components as well as deposition and cross-linking of collagen [81]. Other than collagen, fibronectin is also a component of the ECM, where ITGAV:ITGB5 is one of the receptors for fibronectin. Aging is associated with increased stretching of fibronectin fibrils and ECM maturation. ITGB5 was reported as a putative physiologic activator of TGF-β, leading to activation of ECM-bound latent TGF-β1 by traction. Consistently, *ITGB5* knockout demonstrated the absence of TGF-β-related phenotype. The most putative TGF-β activators are functionally associated with the ECM [82]. TGF-β signaling, being downstream of other signals, was shown to repress body size as well as lifespan *in vivo* [83]. Notably, ITGB5 knockdown did not affect the proliferation of human adipose-derived stem cells [84], suggesting minimal cell toxicity induced. Therefore, suppressing ITGB5 may provide new insights for aging treatment. Taken together, inhibition of CXCL12, SPP1, ITGB5 and ADAMTS14 may provide a promising therapeutic approach for aging and AADs.

Epigenetic reprogramming is one of the most promising areas in longevity [85]. In line with this notion, 13 of our targets (*HDAC1, HDAC9, EP300, KAT6A, KAT8, KDM7A, EZH2, DNMT1, SIRT1, MTOR, IGF1, AKT1*, and *MYO1C*) were associated with the epigenetic shift aging hallmark (Figure 3). Histone modification and DNA methylation are the most studied epigenetic phenomena, and these modifications are accumulating over the life course. Histone deacetylases HDAC1 and HDAC9 are markers of epigenetic transcriptional repression. Whereas histone acetyltransferases EP300, KAT6A, and KAT8 enhance epigenetic transcriptional activation [86–89]. Histone demethylase KDM7A specifically demethylates H3K9me2, H3K27me2 and H4K20me1. Histone-lysine N-methyltransferase EZH2 methylates H3K9me and H3K27me, leading to epigenetic transcriptional repression of the affected gene. Some of these epigenetic regulatory enzyme targets were also involved in modulating aging processes. For example, it was reported that KAT8 might alter the function of ATM, which plays a pro-longevity role [90, 91]. In addition, the activities of DNMT1 and SIRT1 were found to be attenuated during aging, leading to alterations of epigenetic landscape, thereby changing gene expression and promoting aging processes [3]. In aging livers, C/EBPβ-HDAC1 complexes repress E2F-dependent promoters and occupy the promoter of GSK3B, resulting in epigenetic silencing of cell cycle genes and altered GSKβ-cyclin D3 pathways, respectively [92]. Collectively, the above evidence reveals the involvement of our target in epigenetic regulation of cellular proliferation and development, and suggests the potential mechanism for the involvement of these targets in aging and AADs. Targeting epigenetic regulation may be one of the promising approaches for healthspan-promotion and life-extension [93].

In conclusion, we successfully established an approach to identify potential dual-purpose targets for aging and AADs, enabling biologists and clinicians to further investigate their therapeutic potential in a cost-saving and time-efficient manner for drug discovery. These promising results underscore the ability of PandaOmics to identify novel targets not only for specific disorders, but across multiple types of diseases.

MATERIALS AND METHODS

Disease and dataset selection

Diseases were selected and classified into either AADs or NAADs based on the consideration of whether age is a strong risk factor for the disease's onset. To obtain a more aging-oriented result, 14 AADs and 19 NAADs were selected (Table 1).

Microarray and RNA-seq datasets for the selected diseases containing case and control samples were retrieved from public repositories and processed by PandaOmics (Supplementary Table 7). A total of 79 and 113 datasets were selected for AADs and NAADs, respectively. For AADs, age information was available in 29 datasets, with 1,223 cases and 819 control samples. For NAADs, age information was available in 35 datasets containing 1,161 cases and 713 control samples. The mean age of cases and controls in AADs was 67.9 (s.d. = 17.50) and 60.91 (s.d. = 21.01), and in NAADs 36.87 (s.d. = 18.29) and 37.20 (s.d. = 19.15), respectively.

Meta-analysis

For each dataset, case and control samples from the same tissue source were selected and compared, resulting in a total of 87 and 126 case-control comparisons for 14 AADs and 19 NAADs, respectively (Table 1). All the case-control comparisons performed for each disease were pooled into a single meta-analysis, yielding a total of 33 meta-analyses for all selected diseases subjected to target identification.

Filter settings for target identification

Targets were prioritized by PandaOmics (available at https://pandaomics.com/) using its AI hypothesis generation models based on 21 scores from Omics, Text-based, Financial, and KOL categories. Additional filters including Druggability (small molecules, antibodies, safety, novelty), Tissue specificity, Target family, and Development filters were applied to refine the list to satisfy the user's research goals. In this study, only the genes belonging to the druggable protein class were included. The loss of novelty would be a trade-off for the abundance of evidence connecting a target to a disease. In view of this, a list of target genes in high confidence, medium novelty, and high novelty settings based on the volume of related publications proposed by PandaOmics' proprietary AI engine, as well as the number of clinical trials they have been involved in was identified. A customized set of scores and filters was applied to obtain a list of genes with the associated final ranking, which represents the strength of association between a gene and the disease, for each novelty setting.

Identification of targets implicated in multiple diseases

For each novelty setting, a list of 100 genes with the highest ranking calculated by PandaOmics was extracted from each disease, generating a combined list of genes from 14 AADs, and another from 19 NAADs. The genes were then prioritized by their (1) descending occurrence, and (2) ascending average ranking across multiple diseases, and those top-100 genes were selected for further analysis. Consequently, these selected genes from AADs were overlapped with those from NAADs to classify the genes into AAD targets and common targets, as exemplified in the Venn diagram (Figure 1).

Hallmarks of aging assessment

The 300 genes obtained from the three novelty settings consisting of both AAD targets and common targets were subjected to literature review on PubMed for their association with hallmarks of aging (search terms included in Supplementary Table 2). Studies that matched our search terms composed of all hallmarks and keywords of the corresponding pathways were selected for review. Their association with hallmarks of aging was decided based on their biological functions, pathways, and roles in regulating important pathways or genes associated with aging. All genes associated with hallmarks of aging were included, along with their literature evidence and PubMed ID (Supplementary Table 2). Among the genes included, those that are known cancer drivers were annotated by the data of the NCG7.0 database [33].

Expression levels in age-associated diseases

The values of logFC for the genes in each of the 87 case-control comparisons performed for AADs were calculated. Considering the diverse complexity of mechanisms and pathologies in different diseases, we computed the consistency of each gene's dysregulation state in each of the four disease classes (fibrotic, inflammatory, metabolic, and neurological diseases). Genes that were upregulated or downregulated in 60% or more of case-control comparisons in the disease class were considered as consistently dysregulated. Genes were further investigated provided that they were consistently dysregulated in the same trend in 2 or more disease classes.

Pathway enrichment analysis for identified targets

The 145 genes identified from hallmarks of aging assessment were input to perform pathway enrichment analysis based on the KEGG PATHWAY Database [48] by *clusterProfiler* in R. Pathways with $p < 0.05$ were considered significantly enriched. Aging-associated pathways were further selected for visualization.

Curation of known aging-associated genes

The curation of well-known genes associated with aging was based on the genes targeted by the investigated drugs that entered clinical trials with either aging or healthy aging as one of the disease conditions (http://ClinicalTrials.gov, accessed on 30-DEC-2021), publication and geroprotectors (http://Geroprotectors.org, accessed on 17-FEB-2022) [46]. The curated genes were further refined to druggable genes in PandaOmics by (1) applying the filter of a druggable protein class and (2) adjusting the druggability filter (small molecule score ≥1 and safety score ≥1), yielding the final list of 62, 48 and 52 known aging-associated genes from clinical trials (Supplementary Table 3), publication (Supplementary Table 4) and geroprotectors (Supplementary Table 5),

respectively. In addition, 307 genes associated with aging suggested by the database, GenAge (build 20) [47], were also retrieved and filtered based on the above settings, resulting in 149 genes included for analysis.

Statistical analysis

T-test analysis was performed to compare the logFC (two-tailed) for each gene calculated by PandaOmics between AADs and NAADs. The significant level of target enrichment in the pool of curated aging-associated genes or GenAge genes was estimated using the hypergeometric test as:

$$p = 1 - \sum_{i=0}^{r-1} \frac{\binom{K}{i}\binom{N-K}{n-i}}{\binom{N}{n}}$$

where N equals 5,626 which stands for the total number of druggable genes defined in PandaOmics, K represents the number of aging-associated genes in the interested pool, n is the number of identified targets, and r represents the number of genes shared between the interested pool of aging-associated genes and the list of identified targets.

Abbreviations

ADAMTS14: A disintegrin and metalloproteinase with thrombospondin motifs 14; AAD: Age-associated disease; AI: Artificial Intelligence; ALS: Amyotrophic lateral sclerosis; COPD: Chronic obstructive pulmonary disease; CXCR4: C-X-C Motif Chemokine Receptor 4; CXCL12: C-X-C Motif Chemokine Ligand 12; DEG: Database of essential genes; DNMT1: DNA (cytosine-5)-methyltransferase 1; ECM: Extracellular matrix; FDA: Food and Drug Administration; GHR: Growth Hormone Receptor; HSC: Hematopoietic stem cell; IPF: Idiopathic pulmonary fibrosis; ITGB5: Integrin subunit beta 5; KEGG: Kyoto Encyclopedia of Genes and Genomes; KOL: Key opinion leader; logFC: log-fold change; MMP: Matrix metalloproteinase; MSC: Mesenchymal stem cell; NAAD: Non-age-associated disease; RA: Rheumatoid arthritis; SIRT1: Sirtuin 1; SPP1: Secreted phosphoprotein 1; TLR4: Toll-like receptor 4; OA: Osteoarthritis.

AUTHOR CONTRIBUTIONS

FP performed data analysis, participated in result interpretation and project administration, and drafted the manuscript. GL and HL analyzed data, performed visualization, participated in result interpretation, and drafted the manuscript. BL participated in result interpretation and drafted the manuscript. XL performed the statistical analysis and drafted the manuscript. IO prepared data curation, methodology, and software. JW and FR participated in the result interpretation. AA designed the study and provided resources. EI and AM reviewed the manuscript. JPM participated in result interpretation and drafted the manuscript. AZ provided conceptualization, reviewed the manuscript, provided resources, and supervised the projects. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

FP, GL, HL, BL, XL, IO, JW, FR, AA, and AZ are affiliated with Insilico Medicine, a commercial company developing AI solutions for aging research, drug discovery, and longevity medicine. JPM is a consultant to Insilico Medicine.

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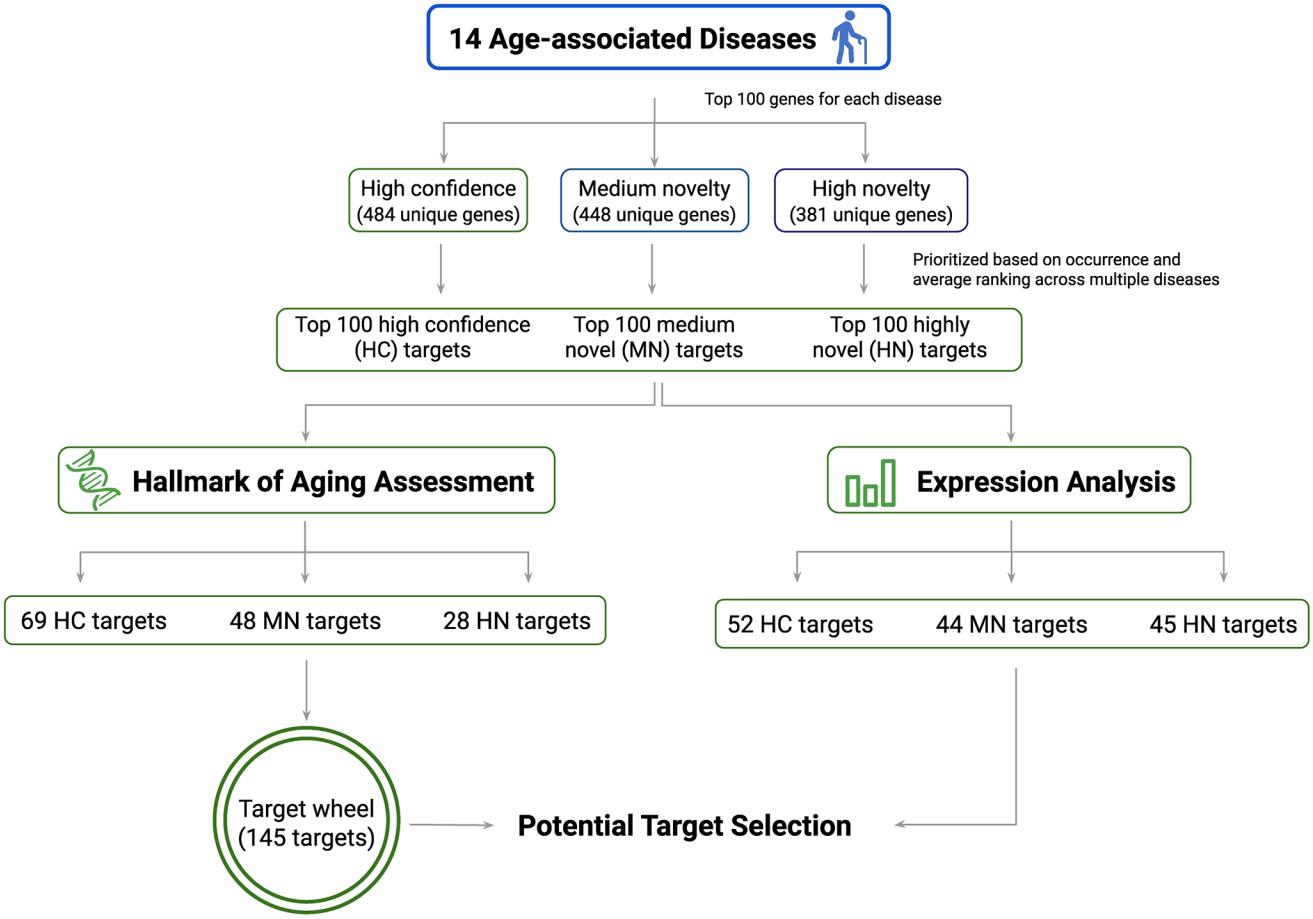
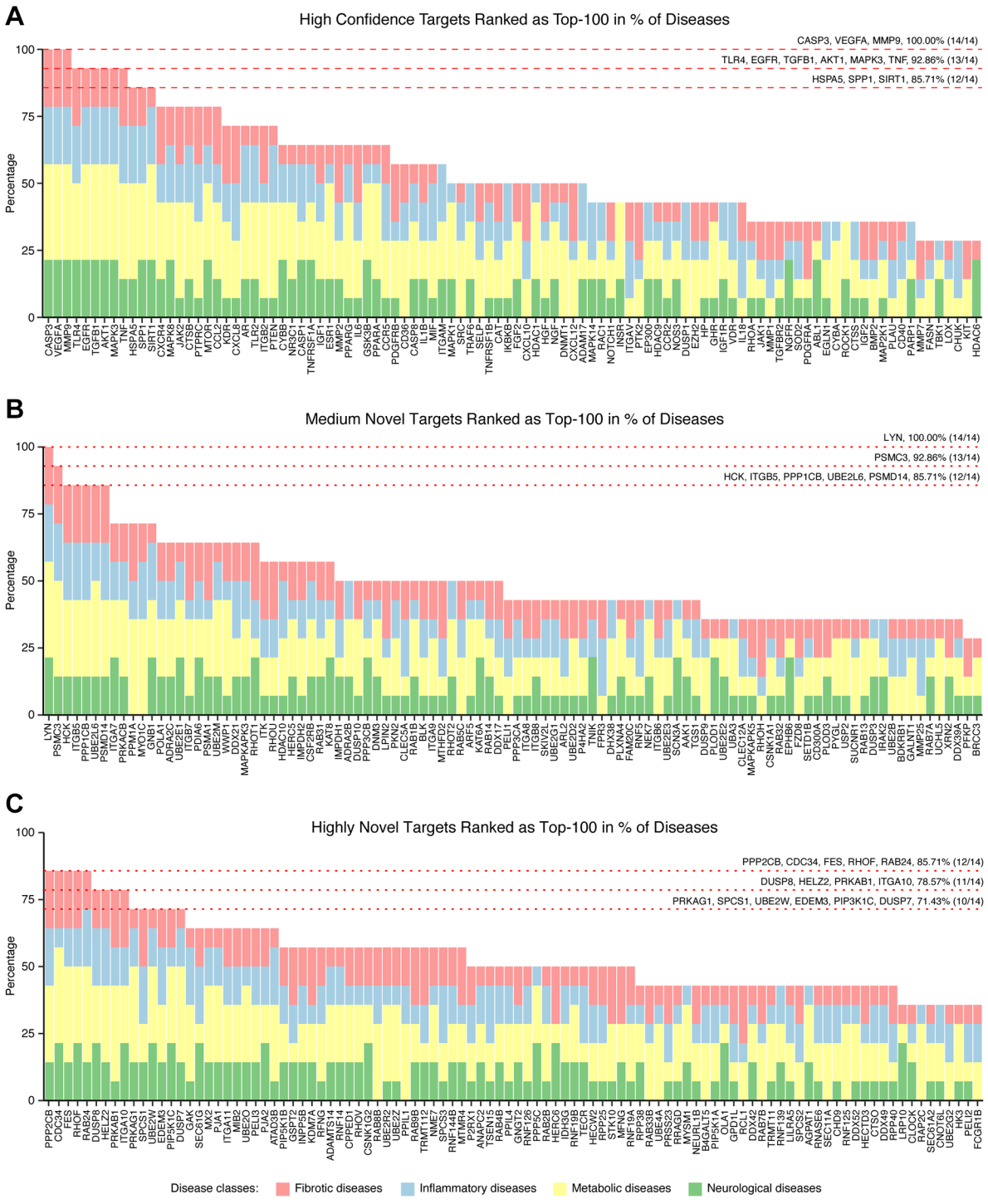
SUPPLEMENTARY MATERIALS

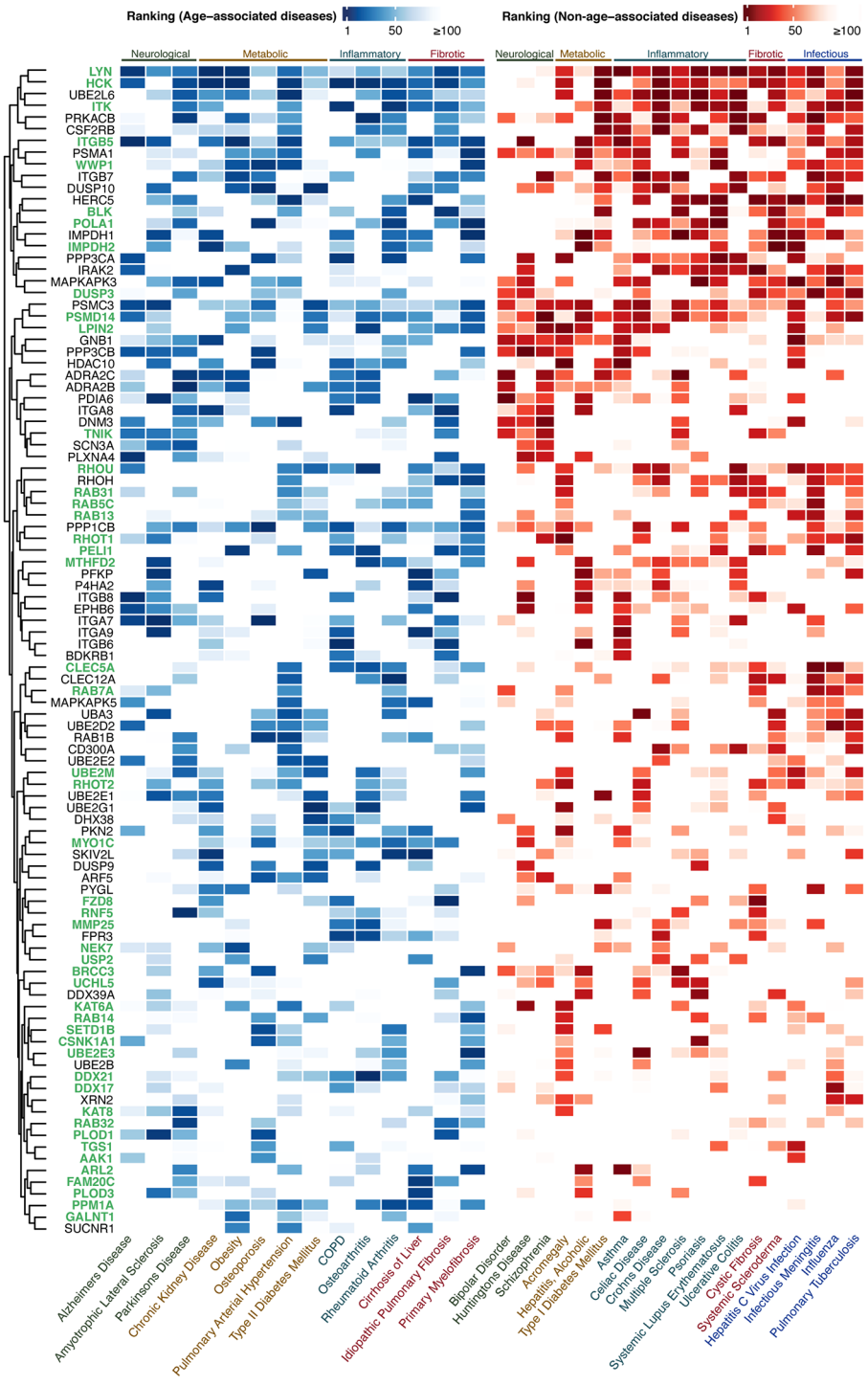
Supplementary Figures



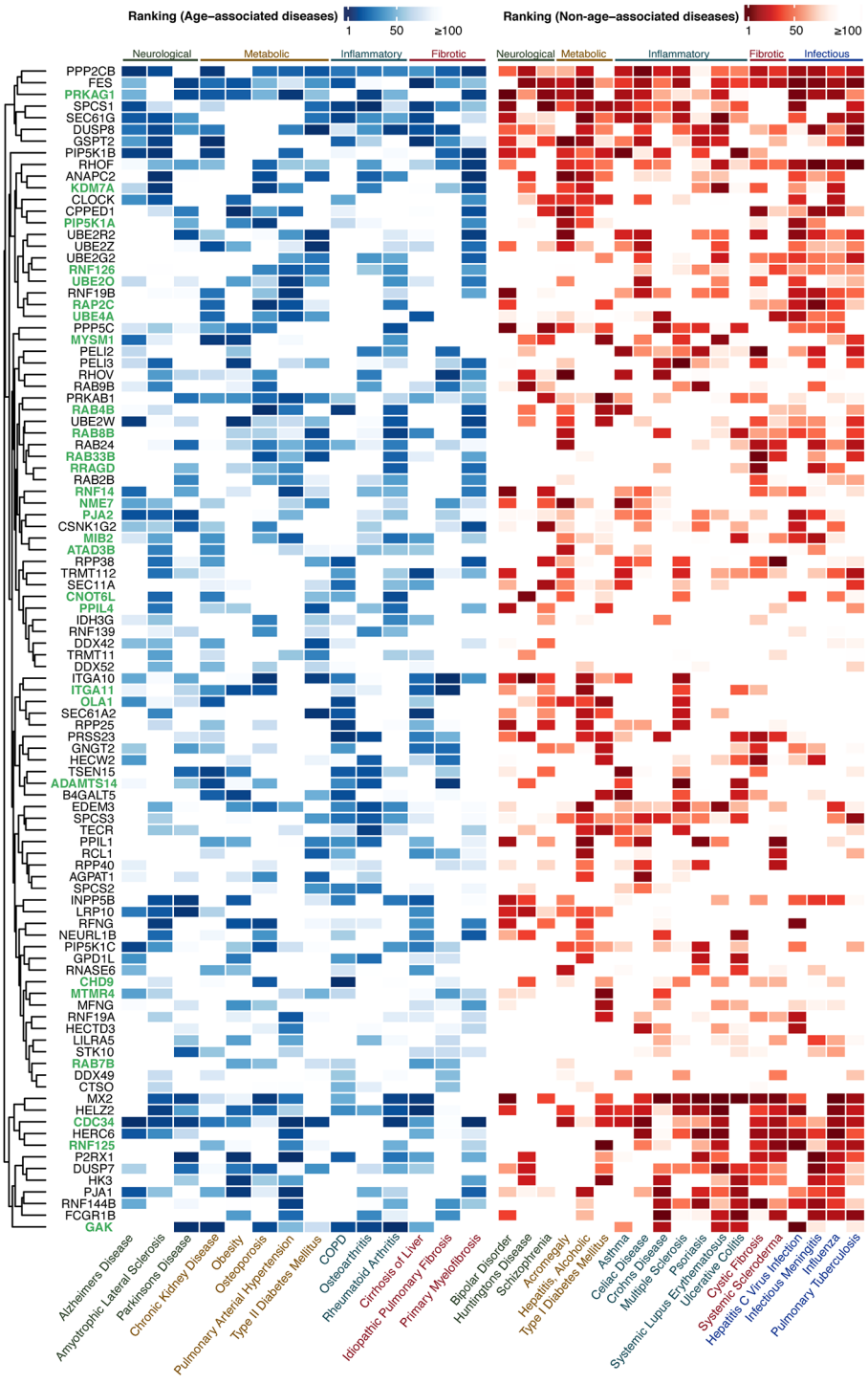
Supplementary Figure 1. Flowchart of the selection of dual-purpose targets from the 14 AADs. Upon target identifications from the 14 AADs, 484 high confidence (HC) targets, 448 medium novel (MN) targets and 381 highly novel (HN) targets were identified by PandaOmics. Targets ranked as top 100 for each novelty (total 300 targets) were subjected to the hallmarks of aging assessment by searching the literature for their evidence in modulating longevity or longevity pathways, and consistency in dysregulated expression across disease classes. A total of 145 targets including 69 HC targets, 48 MN targets and 28 HN targets were associated with aging hallmarks whereas 52 HC targets, 44 MN targets and 45 HN targets were consistently dysregulated in two or more disease classes in a unidirectional manner. Potential dual-purpose candidates were selected with reference to both the hallmarks of aging assessment and expression analysis.



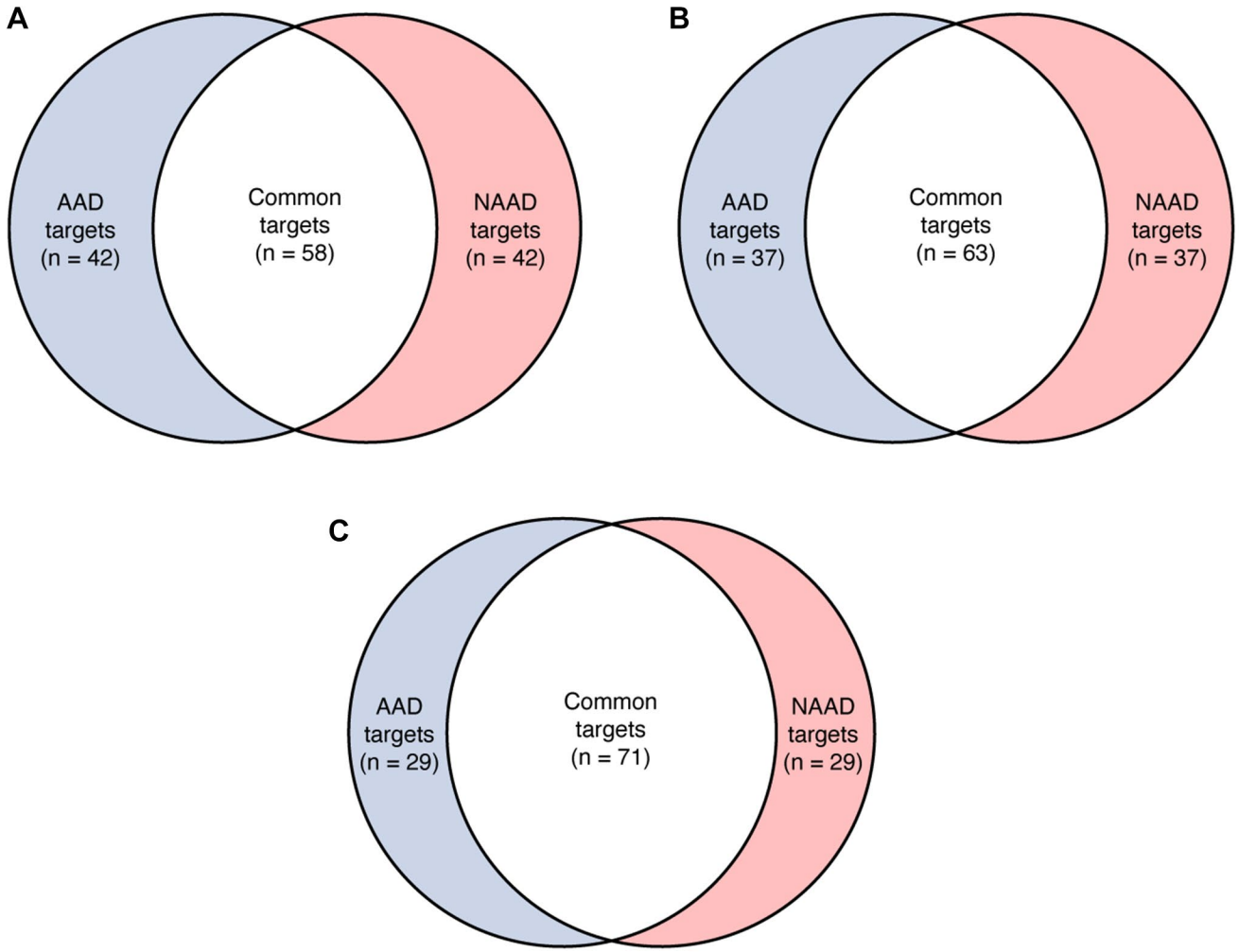
Supplementary Figure 2. Occurrence of the top-100 targets in the 14 AADs. The y-axis indicates the percentage of diseases in which the target was highly ranked (≤100) under (**A**) high confidence, (**B**) medium novel, and (**C**) highly novel filter settings. The targets with the highest percentages are exemplified above the horizontal dashed lines with their occurrence percentages shown in brackets. AADs are colored according to their disease classes.



Supplementary Figure 3. Ranking of the top-100 gene set for AADs under medium novelty settings. The ranking of the targets in AADs or NAADs were colored in blue-white and red-white thermal scales respectively. High color intensity stands for high rankings. The lowest ranking was capped at 100. Targets associated with the hallmark(s) of aging are labeled in green. AADs and NAADs are colored according to their disease classes.



Supplementary Figure 4. Ranking of the top-100 gene set for AADs under high novelty settings. The ranking of the targets in AADs or NAADs were colored blue-white and red-white thermal scales respectively. High color intensity stands for high rankings. The lowest ranking was capped at 100. Targets associated with the hallmark(s) of aging are labeled in green. AADs and NAADs are colored according to their disease classes.



Supplementary Figure 5. Overlapping between the two sets of top-100 genes from AADs and NAADs. Top-ranked targets shared by both AAD and NAAD categories were regarded as common targets, while targets unique to AADs were defined as AAD targets under (**A**) high confidence, (**B**) medium novelty, and (**C**) high novelty filter settings.

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Tables 1, 2, 6 and 7.

Supplementary Table 1. Top-100 genes for each filter setting.

Supplementary Table 2. Genes associated with hallmarks of aging.

Supplementary Table 3. Overlapping of high confidence targets with the pool of curated aging-associated genes from clinical trials.

Gene[1]	Aging clinical trial[2]	Druggability[3]	Target family[4]	Top-100 target[5]
ABL1	DASATINIB (NCT04994561, NCT04946383)	2,0,2,0	Tyrosine kinase	✓
AR	TESTOSTERONE (NCT00182871, NCT00309855, NCT00680797, NCT02203656, NCT02679274, NCT02990533)	2,0,2,0	Nuclear receptor	✓
ESR1	CLIMARA (NCT00220454, NCT02042196)	2,2,2,0	Nuclear receptor	✓
GHR	GROWTH HORMONE RELEASING HORMONE (GHRH) (NCT01410799)	2,2,2,0	Immunoglobulin	✓
IGF1	ORALLY ACTIVE GROWTH HORMONE SECRETAGOGUE (MK-677) (NCT00474279)	2,2,2,0	Growth factor	✓
IGF1R	INSULIN-LIKE GROWTH FACTOR 1 (NCT03932162)	2,2,2,0	Receptor kinase	✓
KIT	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Receptor kinase	✓
MAPK14	DASATINIB (NCT04994561, NCT04946383)	2,0,1,0	CMGC kinase	✓
MTOR	RAPAMYCIN (NCT02874924, NCT04488601, NCT04742777)	2,0,2,0	Protein kinase	✓
NR3C1	METHYLPREDNISOLONE (NCT03529929)	2,0,2,0	Nuclear receptor	✓
PDGFRB	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Receptor kinase	✓
SIRT1	RESVERATROL (NCT02523274)	2,0,2,0	Acyltransferase	✓
SRC	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Tyrosine kinase	✓
VDR	NT-020 (NCT01963767)	2,0,2,0	Nuclear receptor	✓
ACE	PERINDOPRIL (NCT03295734)	2,2,2,0	Glycosylase	
AGTR1	CANDESARTAN (NCT00605072)	2,2,2,0	GPCR	
AMY2A	ACARBOSE (NCT02865499, NCT02953093)	2,0,2,0	Glycosylase	
BCR	DASATINIB (NCT04994561, NCT04946383)	2,2,1,0	Protein kinase	
BST1	NICOTINAMIDE MONONUCLEOTIDE (NCT04823260)	2,2,2,0	Glycosylase	
BTK	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Tyrosine kinase	
CHRNA3	NICOTINE PATCH, ORAL MECAMYLAMINE, PLACEBO (NCT03408574)	2,0,1,0	Ion channel	
CHRNA4	NICOTINE PATCH, ORAL MECAMYLAMINE, PLACEBO (NCT03408574)	2,0,2,0	Ion channel	
CSK	DASATINIB (NCT04994561, NCT04946383)	2,0,2,0	Tyrosine kinase	
EPHA2	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Receptor kinase	
EPHA5	DASATINIB (NCT04994561, NCT04946383)	2,2,1,0	Receptor kinase	
EPHB4	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Receptor kinase	
ETFDH	METFORMIN (NCT01765946, NCT02308228, NCT02432287, NCT03072485, NCT03309007, NCT03451006, NCT03713801, NCT04264897)	2,0,1,0	Oxidoreductase	
FGR	DASATINIB (NCT04994561, NCT04946383)	2,1,2,2	Tyrosine kinase	
FKBP1A	RAPAMYCIN (NCT02874924, NCT04488601, NCT04742777)	2,0,2,0	Isomerase	
FRK	DASATINIB (NCT04994561, NCT04946383)	2,0,1,2	Tyrosine kinase	

FYN	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Tyrosine kinase
GAA	ACARBOSE (NCT02865499, NCT02953093)	2,0,2,0	Glycosylase
GABRA1	ZOLPIDEM (NCT00383357, NCT03657212)	2,0,2,0	Ion channel
GABRA2	ZOLPIDEM (NCT00383357, NCT03657212)	2,0,2,0	Ion channel
GABRA3	ZOLPIDEM (NCT00383357, NCT03657212)	2,0,2,1	Ion channel
GABRB1	ZOLPIDEM (NCT00383357, NCT03657212)	2,0,1,1	Ion channel
GABRG2	ZOLPIDEM (NCT00383357, NCT03657212)	2,0,2,0	Ion channel
GHSR	ORALLY ACTIVE GROWTH HORMONE SECRETAGOGUE (MK-677) (NCT00474279)	2,0,2,0	GPCR
GPD1	METFORMIN (NCT01765946, NCT02308228, NCT02432287, NCT03072485, NCT03309007, NCT03451006, NCT03713801, NCT04264897)	1,0,1,0	Oxidoreductase
GPD2	METFORMIN (NCT01765946, NCT02308228, NCT02432287, NCT03072485, NCT03309007, NCT03451006, NCT03713801, NCT04264897)	2,0,1,0	Oxidoreductase
LCK	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Tyrosine kinase
MGAM	ACARBOSE (NCT02865499, NCT02953093)	2,0,2,0	Glycosylase
NR3C2	TESTOSTERONE (NCT00182871)	2,0,2,0	Nuclear receptor
NR4A3	DASATINIB (NCT04994561, NCT04946383)	1,0,1,0	Nuclear receptor
OXTR	OXYTOCIN NASAL SPRAY (NCT03119610)	2,2,2,0	GPCR
PPAT	DASATINIB (NCT04994561, NCT04946383)	2,0,2,0	Glycosyltransferase
PTGS1	DICLOFENAC (NCT03072485)	2,0,2,0	Oxidoreductase
PTGS2	DICLOFENAC (NCT03072485)	2,2,2,0	Oxidoreductase
SI	ACARBOSE (NCT02865499, NCT02953093)	2,0,1,0	Glycosylase
SRD5A1	DUTASTERIDE (NCT00309855)	2,0,2,0	Oxidoreductase
SRD5A2	DUTASTERIDE (NCT00309855)	2,0,1,0	Oxidoreductase
SRMS	DASATINIB (NCT04994561, NCT04946383)	2,0,1,0	Tyrosine kinase
TERT	AAV-HTERT (NCT04133649)	2,2,2,0	Transferase
YES1	DASATINIB (NCT04994561, NCT04946383)	2,2,2,0	Tyrosine kinase
ABL2	DASATINIB (NCT04994561, NCT04946383)	1,0,1,1	Tyrosine kinase
CHRNB2	NICOTINE PATCH, ORAL MECAMYLAMINE, PLACEBO (NCT03408574)	2,0,2,1	Ion channel
CHRNB4	NICOTINE PATCH, ORAL MECAMYLAMINE, PLACEBO (NCT03408574)	2,0,2,1	Ion channel
SRD5A3	DUTASTERIDE (NCT00309855)	2,2,1,1	Oxidoreductase
BLK*	DASATINIB (NCT04994561, NCT04946383)	2,0,2,1	Tyrosine kinase
HCK*	DASATINIB (NCT04994561, NCT04946383)	2,2,2,1	Tyrosine kinase
LYN*	DASATINIB (NCT04994561, NCT04946383)	2,2,2,1	Tyrosine kinase
PRKAB1^	METFORMIN (NCT01765946, NCT02308228, NCT02432287, NCT03072485, NCT03309007, NCT03451006, NCT03713801, NCT04264897)	2,0,1,2	Protein kinase

[1]Curated pool of aging-associated genes (genes identified as medium novel targets were marked with asterisks, and highly novel targets with arrow heads) Sources of curation was http://ClinicalTrials.gov aging drug targets. [2]Example of drug investigated in aging clinical trials with clinical trial ID shown in parenthesis. Target-drug association were manually curated. [3]Druggability scores defined in PandaOmics (small molecules, antibodies, safety, novelty). [4]Druggable gene classes defined in PandaOmics. [5]Genes identified as top-100 high-confidence targets are marked with ticks.

Supplementary Table 4. Overlapping of high confidence targets with the pool of curated aging-associated genes from publication.

Genes[1]	Gene Name[2]	Druggability[3]	Target family[4]	Top-100 target[5]
AKT1	AKT serine/threonine kinase 1	2,0,2,0	AGC kinase	✓
CASP3	caspase 3	2,0,2,0	Peptidase	✓
CAT	catalase	2,0,2,0	Oxidoreductase	✓
CHUK	component of inhibitor of nuclear factor kappa B kinase complex	2,0,2,0	Protein kinase	✓
DNMT1	DNA methyltransferase 1	2,0,1,0	Methyltransferase	✓
EGFR	epidermal growth factor receptor	2,2,2,0	Receptor kinase	✓
HDAC9	histone deacetylase 9	2,0,1,0	Hydrolase	✓
IGF1	insulin like growth factor 1	2,2,2,0	Growth factor	✓
IGF1R	insulin like growth factor 1 receptor	2,2,2,0	Receptor kinase	✓
IL1B	interleukin 1 beta	2,2,2,0	Interleukin	✓
IL6	interleukin 6	2,2,2,0	Interleukin	✓
JAK2	Janus kinase 2	2,0,2,0	Tyrosine kinase	✓
MAPK8	mitogen-activated protein kinase 8	2,0,2,0	CMGC kinase	✓
MMP1	matrix metallopeptidase 1	2,2,2,0	Peptidase	✓
MMP2	matrix metallopeptidase 2	2,2,2,0	Peptidase	✓
MMP9	matrix metallopeptidase 9	2,2,2,0	Peptidase	✓
MTOR	mechanistic target of rapamycin kinase	2,0,2,0	Protein kinase	✓
PPARA	peroxisome proliferator activated receptor alpha	2,0,2,0	Nuclear receptor	✓
PTEN	phosphatase and tensin homolog	1,1,1,0	Esterase	✓
SIRT1	sirtuin 1	2,0,2,0	Acyltransferase	✓
SOD2	superoxide dismutase 2	1,0,1,0	Oxidoreductase	✓
TGFB1	transforming growth factor beta 1	2,2,2,0	Growth factor	✓
TGFBR2	transforming growth factor beta receptor 2	2,2,2,0	Receptor kinase	✓
TNF	tumor necrosis factor	2,2,2,0	Tumor necrosis factor	✓
ABO	ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase	1,0,1,0	Glycosyltransferase	
AKT2	AKT serine/threonine kinase 2	2,0,2,0	AGC kinase	
BMP1	bone morphogenetic protein 1	1,0,1,0	Peptidase	
GZMB	granzyme B	2,0,2,0	Peptidase	
HAS1	hyaluronan synthase 1	1,2,1,0	Glycosyltransferase	
HAS2	hyaluronan synthase 2	1,0,1,0	Glycosyltransferase	
HDAC11	histone deacetylase 11	2,2,2,0	Hydrolase	
HDAC4	histone deacetylase 4	2,0,2,0	Hydrolase	
IL15	interleukin 15	2,2,2,0	Interleukin	
MME	membrane metalloendopeptidase	2,2,2,0	Peptidase	
MMP13	matrix metallopeptidase 13	2,2,2,0	Peptidase	
MT-ND2	mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 2	2,0,1,0	Translocase	
NOX4	NADPH oxidase 4	2,0,2,0	Oxidoreductase	
PPIA	peptidylprolyl isomerase A	2,0,2,0	Isomerase	
PRDX2	peroxiredoxin 2	1,0,1,0	Oxidoreductase	
PRKCD	protein kinase C delta	2,0,2,0	AGC kinase	

PTGS2	prostaglandin-endoperoxide synthase 2	2,2,2,0	Oxidoreductase
SIRT6	sirtuin 6	2,0,1,0	Acyltransferase
SOD1	superoxide dismutase 1	2,2,2,0	Oxidoreductase
TYR	tyrosinase	2,0,2,0	Oxidoreductase
WNK2	WNK lysine deficient protein kinase 2	1,0,1,0	Protein kinase
XDH	xanthine dehydrogenase	2,0,2,0	Oxidoreductase
AOPEP	aminopeptidase O (putative)	2,0,1,2	Peptidase
CLOCK^	clock circadian regulator	1,0,1,2	Acyltransferase

[1]Curated pool of aging-associated genes (genes identified as medium novel targets are marked with asterisks, and highly novel targets with arrow heads). [2]These genes were associated with aging or skin aging with reference to a publicity database. [3]Druggability scores defined in PandaOmics (small molecules, antibodies, safety, novelty). [4]Druggable gene classes defined in PandaOmics. [5]Genes identified as top-100 high confidence targets were marked with ticks.

Supplementary Table 5. Overlapping of high confidence targets with the pool of curated aging-associated genes from geroprotectors.

Genes[1]	Geroprotectors[2]	Druggability[3]	Target family[4]	Top-100 target[5]
CASP1	Aspirin	2,0,2,0	Peptidase	✓
CASP3	Aspirin	2,0,2,0	Peptidase	✓
CHUK	N-acetyl-L-cysteine	2,0,2,0	Protein kinase	✓
ESR1	17-A-Estradiol; Melatonin	2,2,2,0	Nuclear receptor	✓
HSPA5	Aspirin	2,2,2,0	Hydrolase	✓
IKBKB	Aspirin; N-acetyl-L-cysteine	2,0,2,0	Protein kinase	✓
MTOR	Rapamycin	2,0,2,0	Protein kinase	✓
ACE	Enalapril	2,2,2,0	Glycosylase	
ACY1	N-acetyl-L-cysteine	2,0,2,0	Hydrolase	
ADRB1	Metoprolol; Nebivolol	2,2,2,0	GPCR	
ADRB2	Metoprolol; Nebivolol	2,0,2,0	GPCR	
ADRB3	Nebivolol	2,2,2,0	GPCR	
AKR1C1	Aspirin	1,0,1,0	Oxidoreductase	
ALOX5	Nordihydroguaiaretic Acid	2,0,2,0	Oxidoreductase	
AMY2A	Acarbose	2,0,2,0	Glycosylase	
ASMT	Melatonin	1,0,1,0	Methyltransferase	
CHRNA4	17-A-Estradiol	2,0,2,0	Ion channel	
CKB	Creatine	2,0,1,0	Unclassified kinase	
CKM	Creatine	2,0,1,0	Non-protein kinase	
EDNRA	Aspirin	2,2,2,0	GPCR	
EPX	Melatonin	1,0,1,0	Oxidoreductase	
ESR2	17-A-Estradiol	2,0,2,0	Nuclear receptor	
ETFDH	Metformin	2,0,1,0	Oxidoreductase	
GAA	Acarbose	2,0,2,0	Glycosylase	
GAMT	Creatine	2,0,1,0	Methyltransferase	
GPD1	Metformin	1,0,1,0	Oxidoreductase	
GPER1	17-A-Estradiol	1,0,1,0	GPCR	
GRIN1	N-acetyl-L-cysteine	2,0,1,0	Ion channel	
GRIN2A	N-acetyl-L-cysteine	2,0,1,0	Ion channel	
GRIN2B	N-acetyl-L-cysteine	2,0,2,0	Ion channel	

GRIN2D	N-acetyl-L-cysteine	2,0,1,0	Ion channel
GRIN3A	N-acetyl-L-cysteine	2,0,1,0	Ion channel
GSS	N-acetyl-L-cysteine	2,0,1,0	Ligase
IFNG	D-Glucosamine	2,2,2,0	Interferon
MAOA	Deprenyl or Selegiline	2,0,2,0	Oxidoreductase
MAOB	Deprenyl or Selegiline	2,0,2,0	Oxidoreductase
MGAM	Acarbose	2,0,2,0	Glycosylase
MPO	Melatonin	2,0,2,0	Oxidoreductase
MTNR1A	Melatonin	2,0,2,0	GPCR
MTNR1B	Melatonin	2,0,2,0	GPCR
NEU1	Aspirin	1,0,1,0	Glycosylase
NPY2R	Cysteamine	2,0,2,0	GPCR
NQO2	Melatonin	2,0,2,0	Oxidoreductase
NR1I2	17-A-Estradiol	2,0,2,0	Nuclear receptor
PTGS1	Aspirin	2,0,2,0	Oxidoreductase
PTGS2	Aspirin	2,2,2,0	Oxidoreductase
RPS6KA3	Aspirin	2,0,2,0	AGC kinase
SI	Acarbose	2,0,1,0	Glycosylase
CKMT1A	Creatine	2,0,1,1	Unclassified kinase
CKMT2	Creatine	2,0,1,1	Unclassified kinase
RORB	Melatonin	2,0,2,1	Nuclear receptor
PRKAB1^	Metformin	2,0,1,2	Protein kinase

[1]Curated pool of geroprotector-associated genes (genes identified as medium novel targets are marked with asterisks, and highly novel targets with arrow heads). [2]These geroprotectors were (1) approved drugs for human use and (2) investigated for antiaging effects using human or animal models (with reference to http://geroprotectors.org). Target-drug association were manually curated. [3]Druggability scores defined in PandaOmics (small molecules, antibodies, safety, novelty). [4]Druggable gene classes defined in PandaOmics. [5]Genes identified as top-100 high confidence targets were marked with ticks.

Supplementary Table 6. Pathway enrichment analysis based on 145 targets associated with the hallmarks of aging.

Supplementary Table 7. List of AAD and NAAD datasets analyzed.

Supplementary Table 8. The identification of target-target interactions.

Targets interactions[1]	Reference (PMID)
ROCK1-c-Myc	30613282
FOXO-SIRT3	27686535
mTOR-STAT3	26697523
mTOR-TFEB	30120233
mTOR-PPARG	27901044
MAPK14-c-Myc	10623602
MAPK8-c-Myc	10623602
MAPK-CREB	30214393
MAPK-NRF2	31221142
KDM7A-Catenin beta-1	30614617
KDM7A-Catenin beta-1	32214833

[1]Targets interactions were identified outside the context of pathways with KEGG pathway database.