Table S1. Disease and dataset selection

Solid cancers (n = 11)	Number of dataset con	nparison: Number of cases	Number of controls	
Adrenal cortex carcinoma	6	198	42	GSE10927, GSE12368, GSE19750, GSE33371, GSE75415, GSE90713
Breast carcinoma	19	2,424	739	GSE10780, GSE115144, GSE120129, GSE17907, GSE31448, GSE36295 GSE38959, GSE57297, GSE5764, GSE58135, GSE59246, GSE61304, GSE61723, GSE65212, GSE70905, GSE70947, GSE71651, GSE83591, TCGA-BRCA
Colorectal carcinoma	19	1,211	523	E-MTAB-57, GSE123390, GSE18105, GSE20842, GSE21510, GSE22598 GSE28866, GSE32323, GSE41657, GSE4183, GSE44076, GSE62932 GSE68468, GSE75548, GSE76855, GSE77199, GSE89076, PDC000116 TCGA-COADREAD
Endometrial cancer	7	786	102	GSE115810, GSE17025, GSE36389, GSE56087, GSE63678, PDC000125 TCGA-UCEC
Esophageal carcinoma	8	473	188	GSE1420, GSE161533, GSE20347, GSE23400, GSE70409, GSE74553 GSE75241, TCGA-ESCA
Gastric carcinoma	20	1,111	698	E-MTAB-1440, GSE103236, GSE118897, GSE122401, GSE13195, GSE13911 GSE19826, GSE27342, GSE29272, GSE29998, GSE30727, GSE33335 GSE37023, GSE37023, GSE51575, GSE56807, GSE63089, GSE79973 GSE85465, TCGA-STAD
Hepatocellular carcinoma	13	1,118	651	E-MTAB-5905, GSE102079, GSE107170, GSE19665, GSE36376, GSE45267 GSE59259, GSE60502, GSE6764, GSE67764, GSE82177, PDC000198 TCGA-LIHC
Lung cancer	23	2,457	1,012	E-MEXP-231, E-MTAB-1690, E-MTAB-3950, E-MTAB-5231, GSE104854 GSE18842, GSE19188, GSE19804, GSE28866, GSE30219, GSE40791 GSE43458, GSE44077, GSE63459, GSE74706, GSE75324, GSE83227 GSE84776, PDC000153, PDC000219, PDC000234, TCGA-LUAD, TCGA- LUSC
Ovarian carcinoma	5	112	28	GSE10971, GSE124766, GSE146553, GSE27651, GSE36668
Pancreatic carcinoma	15	595	301	GSE136569, GSE141873, GSE143754, GSE15471, GSE16515, GSE18670 GSE22780, GSE28735, GSE55643, GSE56560, GSE60646, GSE62165 GSE62452, GSE63111, PDC000270
Prostate adenocarcinoma	6	818	147	E-MTAB-6128, GSE111320, GSE68555, GSE6956, PXD010744, TCGA- PRAD

CTEs healthy tissue (a = 47:Number of all samplesNumber of young r Number of old group (aged 60-79)Adipose subcutaneous 663 213237Adipose subcutaneous 643 1175182Adrenal gland*2588881Artery aorta432143140Artery coronary240 63 82Artery tibial 663 232215Brain anygalal1522285Brain anygala1522285Brain caudae basal ganglia24638135Brain cerebellum24139127Brain cerebellum24139127Brain cerebellum24139127Brain cortex bay20926120Brain cortex bay20925117Brain nucleus accumbens bas 24636135Brain putamen basal ganglia2025Colon ransverse459165Colon sigmoid*-373129Colon sigmoid*-373129Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206Easophagus muscularis515206 <th>TOTAL</th> <th>141</th> <th>11,303</th> <th>4,431</th>	TOTAL	141	11,303	4,431
Adress visceral omentum \$41 175 182 Adrenal gland* 258 88 81 Artery aorta 432 143 140 Artery coronary 240 63 82 Artery tibial 663 232 215 Brain amyedala 152 22 85 Brain anterior cingulate corte 176 32 103 Brain cerbeblar hemisphere 215 31 119 Brain cerbeblar hemisphere 215 42 136 Brain cerbeblar 241 39 127 Brain terbeblar 241 39 127 Brain torebolamus 246 136 Brain hippocampus 197 31 114 Brain hippocampus 197 31 143 Brain patame basal ganglia 205 29 109 Brain spinal cortex tos9 209 25 117 Brain spinal cortex formed tympl 174 70 50 Colon sigmoid*^ 373 129 135 Brain substantini gra 139 23<	GTEx healthy tissue (n = 4'	Number of all samples	Number of young g	Number of old group (aged 60-79)
Adrenal gland* 258 88 81 Artery aorta 432 143 140 Artery orony 240 63 82 Artery oron'ny 240 63 82 Artery oron'ny 240 63 82 Artery oron'ny 240 63 82 Brain anterior cingulate corter 16 32 103 Brain arcerollar hemisphere 215 31 119 Brain cerebellum 241 39 127 Brain forottal cortex ba9 209 26 120 Brain forottal cortex ba9 209 26 120 Brain inforotal cortex ba9 202 25 117 Brain indrebus accumbens bas 246 36 135 Brain spinal cord cervical c-1159 22 90 Brain spinal cord cervical c-1159 23 81 Breast margumany tissue* 459 165 Colon tarswerse 406 155 Colon sigmoid*^ 373 129 Esophagus mucosa* 555 206 Colon tarswerse 406 <td>Adipose subcutaneous</td> <td>663</td> <td>213</td> <td>237</td>	Adipose subcutaneous	663	213	237
Artery aorta 432 143 140 Artery voronary 240 63 82 Artery vibia 663 232 215 Brain ananygdala 152 22 85 Brain anterior cingulate corte 176 32 103 Brain ceudate basal ganglia 246 38 135 Brain cerebellar hemisphere 215 31 119 Brain cerebellar bensiphere 215 31 136 Brain cerebellar bensiphere 215 31 143 Brain fortal cortex bas9 209 26 120 Brain hippocampus 197 31 144 Brain pytobalamus 202 25 117 Brain nucleus accumbens bas246 36 135 Brain spinal cord cervical c-1159 22 90 Brain substantia nigra 139 23 81 Breast mammary tissue* 459 165 155 Colon ramsverse 406 155 155 Colon ramsverse 406 165 105 Esophagus mucosa* 555	Adipose visceral omentum	541	175	182
Artery coronary 240 63 82 Artery ibial 663 232 215 Brain anygolal 152 22 85 Brain anygolal 246 38 135 Brain caudate basal ganglia 246 38 135 Brain cerebellar hemisphere 215 31 119 Brain cortex 255 42 136 Brain cortex 255 42 136 Brain cortex 25 114 14 Brain pipocampus 197 31 114 Brain pipocampus 197 31 114 Brain potentas accumbens bas246 36 135 Brain potentas accumbens bas246 136 135 Brain spinal cord cervical -1 159 22 90 Brain spinal cord cervical -21 159 23 81 Breast manmary tissue* 459 165 155 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus muscularis 515 206 143	Adrenal gland*	258	88	81
Artery tibia 663 232 215 Brain amygdala 152 22 85 Brain anterior cingulate corte 176 32 103 Brain cerebellar hemisphere 215 31 119 Brain cerebellar hemisphere 215 31 119 Brain cerebellar benisphere 215 31 114 Brain hippocampus 197 31 114 Brain hippotamblamus 202 25 117 Brain nucleus accumbens bas 246 36 135 Brain putame basal ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain spinal cord cervical c-1 159 23 81 Breas marmary tissue* 459 165 155 Cells ebv-Transformed lympl 174 70 50 Colon signoid*^ 373 129 135 Colon transverse	Artery aorta	432	143	140
Brain anygdal 152 22 85 Brain anterior cingulate corte 176 32 103 Brain ecudate basal ganglia 246 38 135 Brain cortex 215 31 119 Brain cortex 255 42 136 Brain cortex 255 42 136 Brain fornal cortex ba9 209 26 120 Brain fornal cortex ba9 202 25 117 Brain nucleus accumbens bas 246 36 135 Brain putamen basal ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain spinal cord cervical c-1 159 23 81 Breast mammary tissue* 459 165 155 Colon signoid*/ 373 129 135 Colon signoid*/ 373 129 135 Esophagus muscoal*/s 555 206 143 Heart left ventricle 432 146 166 Esophagus muscularis 515 206 143 Heart left ventricle 432 </td <td>Artery coronary</td> <td>240</td> <td>63</td> <td>82</td>	Artery coronary	240	63	82
Brain audie oric 176 32 103 Brain caudate basal ganglia 246 38 135 Brain cerebellar hemisphere 215 31 119 Brain cerebellum 241 39 127 Brain cortex 255 42 136 Brain frontal cortex ba9 209 26 120 Brain notelocampus 197 31 114 Brain nucleus accumbens bas/246 36 135 Brain nucleus accumbens bas/246 36 135 Brain substantia niga 139 22 90 Brain substantia niga 139 23 81 Breast mamary tissue* 459 165 155 Colon sigmoid*^ 373 129 135 Colon ransverse 406 165 105 Esophagus muscolaris 515 206 143 Heart drid appendage 429 95 186 Esophagus muscularis 515 206 143 Heart left ventricle 432 114 164 Liver* 226 59	Artery tibial	663	232	215
Brain caudate basal ganglia 24 38 135 Brain cerebellar hemispher 215 31 119 Brain cerebellar hemispher 215 32 136 Brain cerebellar hemispher 255 42 136 Brain fontal cortex 255 42 136 Brain fippocampus 197 31 114 Brain hippocampus 197 31 114 Brain potamen basal ganglia 202 25 117 Brain putamen basal ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain spinal cord cervical c-1 159 22 90 Brain substantia nigra 139 23 81 Breast mammary tissuef 459 165 155 Colon sigmoid*^ 37 129 135 Colon sigmoid*^ 355 208 166 Esophagus muscularis 515 206 143 Heart left ventricle 432 164 144 Liver* 26 59 84 Lurg*	Brain amygdala	152	22	85
Brain cerebellur hemisphere 215 31 119 Brain cerebellum 241 39 127 Brain cortex 255 42 136 Brain forlat cortex bag 209 26 120 Brain forlat cortex bag 209 25 117 Brain forlat cortex bag 202 25 117 Brain nucleus accumbens bas246 36 135 Brain spinal cord cervical c-1 159 22 90 Brain substantia nigra 139 23 81 Breast mamary tissues 459 165 155 Cells ebv-Transformed lymp! 174 70 50 Colon sigmoid*^ 373 129 135 Colon sigmoid* 373 129 135 Esophagus satrocsophageal 375 135 103 Esophagus muscularis 515 206 143 Heart feit vertricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60	Brain anterior cingulate corte	e 176	32	103
Brain cortex 241 39 127 Brain cortex 255 42 136 Brain frontal cortex ba9 209 26 120 Brain hippocampus 197 31 114 Brain nucleus accumbens bas 246 36 135 Brain putamen basal ganglia 205 29 109 Brain spinal cord cervical c-1159 22 90 Brain spinal cord cervical c-1159 23 81 Breast mammary tissue* 459 165 155 Colon sigmoid*^ 373 129 135 Colon sigmoid*^ 373 129 135 Esophagus gastroesophageal 375 135 103 Esophagus muscularis 515 206 143 Heart left ventricle 432 114 164 Liver* 226 59 84 Lurg* 578 166 212 Minor salivary gland 162 60 52 Minos ekeletal 803 256 292	Brain caudate basal ganglia	246	38	135
Brain cortex 255 42 136 Brain frontal cortex ba9 209 26 120 Brain hippocampus 197 31 114 Brain hypothalamus 202 25 117 Brain nucleus accumbens bas 246 36 135 Brain spinal cord cervical c-1 159 22 90 Brain substattia nigra 139 23 81 Breast mamary tissue* 459 165 155 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus muccoa*^ 555 208 166 Esophagus muccoa* 555 208 166 Esophagus muccoa*/ 555 208 166 Heart atrial appendage 429 95 180 Heart eff ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60	Brain cerebellar hemisphere	215	31	119
Brain frontal cortex ba9 209 26 120 Brain hippocampus 197 31 114 Brain hypothalamus 202 25 117 Brain nucleus accumbers bas 246 36 135 Brain putamen basa ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain substantia nigra 139 23 81 Breast mammary tissue* 459 165 155 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus gus mucosa*^ 555 208 164 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Brain cerebellum	241	39	127
Brain hippocampus 197 31 114 Brain hypothalamus 202 25 117 Brain nucleus accumbens bas 246 36 135 Brain putamen basal ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain substantin airga 139 23 81 Breast mammary tissue* 459 165 155 Cells ebv-Transformed lympl 174 70 50 Colon rainsverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus mucoca*^ 555 208 166 Esophagus muscularis 515 206 143 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 212 Muscle skeletal 803 256 292	Brain cortex	255	42	136
Brain hypothalamus20225117Brain nucleus accumbens bas 24636135Brain putamen basal ganglia20529109Brain spinal cord cervical c-1 1592290Brain substantia nigra1392381Breast mammary tissue*459165155Cells ebv-Transformed lympl 1747050Colon sigmoid*^373129135Colon transverse406165105Esophagus gastroesophageal375135103Esophagus mucscularis515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Brain frontal cortex ba9	209	26	120
Brain nucleus accumbens bas 24636135Brain putamen basal ganglia 20529109Brain spinal cord cervical c-1 1592290Brain substantia nigra1392381Breast mammary tissue*459165155Cells ebv-Transformed lympl 1747050Colon sigmoid*^373129135Colon transverse406165105Esophagus gastroesophageal 375135103Esophagus mucosa*^555208166Esophagus mucularis515206143Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Brain hippocampus	197	31	114
Brain putamen basal ganglia 205 29 109 Brain spinal cord cervical c-1 159 22 90 Brain substantia nigra 139 23 81 Breast mammary tissue* 459 165 155 Cells ebv-Transformed lympl 74 70 50 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastreesophageal 375 135 103 Esophagus mucosa*^ 555 208 166 Esophagus mucosa*^ 515 206 143 Heart tarial appendage 429 95 180 Heart tertiel ventriele 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Brain hypothalamus	202	25	117
Brain spinal cord cervical c-1 1592290Brain substantia nigra1392381Breast mammary tissue*459165155Cells ebv-Transformed lympl 1747050Colon sigmoid*^373129135Colon transverse406165105Esophagus gastroesophageal375135103Esophagus mucosa*^555208166Esophagus mucosa*^515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Brain nucleus accumbens bas	s 246	36	135
Brain substantia nigra 139 23 81 Breast mammary tissue* 459 165 155 Cells ebv-Transformed lympl 174 70 50 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus mucosa*^ 555 208 166 Esophagus muscularis 515 206 143 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Brain putamen basal ganglia	205	29	109
Breast mammary tissue* 459 165 155 Cells ebv-Transformed lympl 74 70 50 Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus mucosa*^ 555 208 166 Esophagus mucularis 515 206 143 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Brain spinal cord cervical c-1	1 1 5 9	22	90
Cells ebv-Transformed lympl 1747050Colon sigmoid*^373129135Colon transverse406165105Esophagus gastrosophageal 375135103Esophagus mucosa*^555208166Esophagus muscularis515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Brain substantia nigra	139	23	81
Colon sigmoid*^ 373 129 135 Colon transverse 406 165 105 Esophagus gastroesophageal 375 135 103 Esophagus mucosa*^ 555 208 166 Esophagus muscularis 515 206 143 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Breast mammary tissue*	459	165	155
Colon transverse406165105Esophagus gastroesophageal375135103Esophagus mucosa*^555208166Esophagus muscularis515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Cells ebv-Transformed lympl	174	70	50
Esophagus gastroesophageal 375 135 103 Esophagus mucosa*^ 555 208 166 Esophagus muscularis 515 206 143 Heart atrial appendage 429 95 180 Heart left ventricle 432 114 164 Liver* 226 59 84 Lung* 578 166 212 Minor salivary gland 162 60 52 Muscle skeletal 803 256 292	Colon sigmoid*^	373	129	135
Esophagus mucosa*^555208166Esophagus muscularis515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Colon transverse	406	165	105
Esophagus muscularis515206143Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Esophagus gastroesophageal	375	135	103
Heart atrial appendage42995180Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Esophagus mucosa*^	555	208	166
Heart left ventricle432114164Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Esophagus muscularis	515	206	143
Liver*2265984Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Heart atrial appendage	429	95	180
Lung*578166212Minor salivary gland1626052Muscle skeletal803256292	Heart left ventricle	432	114	164
Minor salivary gland1626052Muscle skeletal803256292	Liver*	226	59	84
Muscle skeletal 803 256 292	Lung*	578	166	212
Muscle skeletal 803 256 292	Minor salivary gland	162	60	52
Nerve tibial 619 200 229		803	256	292
	Nerve tibial	619	200	229
Ovary* 180 73 46	Ovary*	180	73	46
Pancreas* 328 126 84	Pancreas*	328	126	

Pituitary	283	41	155
Prostate*	245	93	80
Skin not sun exposed	suprapi 604	188	226
Skin sun exposed low	ver leg 701	223	260
Small intestine termin	nal ileun 187	85	46
Spleen	241	101	54
Stomach*	359	147	84
Testis	361	119	125
Thyroid	653	208	234
Uterus*	142	69	28
Vagina	156	64	42
Whole blood	755	249	272
TOTAL	16,740	5,124	6,214

* Tissues corresponding to the 11 studied cancers
 ^ Colon sigmoid and esophagus mucosa were selected as they are the prevalent primary sites for the corresponding cancers

Table S2. Age-associated expression changes in protein-coding genes and cancer-related genes in 47 GTEx tissues

GTEx healthy tissues[1]		Prote	in-coding genes[2]		Tumor suppressor genes[3]						
	Number of genes	Number of	Number of	Number of	Number of genes	Number of	Numebr of	Numebr of			
	sequenced	dysregulation	upregulation	downregulation	sequenced	dysregulation	upregulation	downregulation			
Adrenal gland*	15,690	4,406 (28.08%)	948	3,458	247	85 (34.41%)	17	68			
Breast mammary tissue*	15,939	4,321 (27.11%)	1,525	2,796	245	65 (26.53%)	34	31			
Colon sigmoid*^	15,865	6,185 (38.99%)	2,453	3,732	250	112 (44.8%)	24	88			
Esophagus mucosa*^	15,796	9,436 (59.74%)	2,500	6,936	246	168 (68.29%)	24	144			
Liver*	15,483	1,482 (9.57%)	503	979	247	12 (4.86%)	3	9			
lung*	16,104	8,495 (52.75%)	4,009	4,486	250	143 (57.2%)	82	61			
)vary*	15,757	4,519 (28.68%)	2,163	2,356	246	82 (33.33%)	25	57			
ancreas*	15,702	1,770 (11.27%)	339	1,431	248	34 (13.71%)	5	29			
Prostate*	16,203	5,048 (31.15%)	2,713	2,335	251	74 (29.48%)	48	26			
tomach*	15,860	2,393 (15.09%)	376	2,017	250	45 (18%)	6	39			
Iterus*	15,766	6,944 (44.04%)	1,777	5,167	244	116 (47.54%)	26	90			
Adipose subcutaneous	15,697	8,598 (54.77%)	1,952	6,646	245	145 (59.18%)	29	116			
Adipose visceral omentum	15,786	8,470 (53.66%)	3,227	5,243	245	141 (57.55%)	45	96			
rtery aorta	15,547	8,177 (52.6%)	1,875	6,302	246	152 (61.79%)	27	125			
rtery coronary	15,703	2,309 (14.7%)	391	1,918	247	41 (16.6%)	7	34			
Artery tibial	15,345	11,245 (73.28%)	1,662	9,583	245	202 (82.45%)	25	177			
rain amygdala	15,953	5,489 (34.41%)	1,368	4,121	248	88 (35.48%)	35	53			
brain anterior cingulate cortex ba24	16,068	3,598 (22.39%)	682	2,916	248	58 (23.39%)	15	43			
rain caudate basal ganglia	16,068	3,093 (19.25%)	697	2,396	249	42 (16.87%)	7	35			
Brain cerebellar hemisphere	15,896	2,652 (16.68%)	746	1,906	249	42 (16.87%)	12	30			
rain cerebellum	16,008	3,240 (20.24%)	1,026	2,214	251	51 (20.32%)	16	35			
rain cortex	16,150	4,672 (28.93%)	1,501	3,171	249	68 (27.31%)	21	47			
rain frontal cortex ba9	16,070	5,742 (35.73%)	1,941	3,801	249	93 (37.35%)	33	60			
rain hippocampus	15,996	4,841 (30.26%)	1,082	3,759	248	71 (28.63%)	23	48			
Brain hypothalamus	16,194	4,356 (26.9%)	822	3,534	249	76 (30.52%)	15	61			
Brain nucleus accumbens basal ganglia	16,071	2,234 (13.9%)	838	1,396	249	37 (14.86%)	7	30			
rain putamen basal ganglia	15,930	1,371 (8.61%)	396	975	249	12 (4.84%)	2	10			
Brain spinal cord cervical c-1	15,930	416 (2.61%)	278	138	248	9 (3.63%)	7	2			
Brain substantia nigra	15,905	1040 (6.54%)	288	752	248	16 (6.45%)	4	12			
Cells ebv-Transformed lymphocytes	15,037	1040 (0.5476)	288 967	125	248	13 (5.33%)	13	0			
Colon transverse	16,099	10,040 (62.36%)	6,254	3,786	251	141 (56.18%)	77	64			
	15,695	, , ,	1,377		249	· /	19	108			
sophagus gastroesophageal junction sophagus muscularis	15,686	6,817 (43.43%) 8,008 (51.05%)	1,539	5,440 6,469	249 249	127 (51%) 143 (57.43%)	19	108			
		, , ,	,		249	· · · · ·		123 54			
leart atrial appendage	15,576	4,561 (29.28%)	1,257	3,304		76 (30.77%)	22				
leart left ventricle	15,194	6,920 (45.54%)	1,811	5,109	244	113 (46.31%)	25	88			
finor salivary gland	16,094	4,925 (30.6%)	1,198	3,727	247	77 (31.17%)	8	69			
fuscle skeletal	15,090	9,728 (64.47%)	1,923	7,805	241	169 (70.12%)	31	138			
Verve tibial	15,917	8,537 (53.63%)	2,253	6,284	246	129 (52.44%)	42	87			
Pituitary	16,376	1,408 (8.6%)	827	581	248	18 (7.26%)	15	3			
Skin not sun exposed suprapubic	16,067	6,100 (37.97%)	3,235	2,865	247	102 (41.3%)	71	31			
Skin sun exposed lower leg	16,085	6,269 (38.97%)	1,706	4,563	248	111 (44.76%)	34	77			

Small intestine terminal ileum	16,179	1,852 (11.45%)	1,226	626	250	35 (14%)	15	20
Spleen	15,873	2,514 (15.84%)	1,226	1,288	245	40 (16.33%)	18	22
Testis	17,631	3,075 (17.44%)	995	2,080	252	54 (21.43%)	9	45
Thyroid	15,955	6,759 (42.36%)	1,689	5,070	245	127 (51.84%)	22	105
Vagina	15,955	5,724 (35.88%)	1,400	4,324	249	98 (39.36%)	9	89
Whole blood	14,375	9,464 (65.84%)	3,955	5,509	239	161 (67.36%)	82	79

[1] Tissues corrsponding to the 11 studied cancers were marked with an asterisk. ^ Colon sigmoid and esophagus mucosa were selected as they are the prevalent primary sites for the corresponding cancers

[2] A total of 19,334 protein coding genes

[3] A total of 252 tumor suppressor genes

Table S3. The list of tumor suppressor genes analyzed
ABI1
ACVR1B
ACVR2A
AMER1
APC
ARHGAP26
ARHGEF10
ARHGEF10L
ARHGEF12
ARID1A
ARID1B
ARID2
ASXL1
ASXL2
ATM
ATP2B3
ATR
ATRX
AXIN1
AXIN2
B2M
BAP1
BARD1
BAX
BAZ1A
BCL10
BCOR
BLM
BRCA1
BRCA2

BRIP1 BTG1 BUB1B CAMTA1 CASP3 CASP8 CASP9 CBFA2T3 CBFB CBLB CCDC6 CCNB1IP1 CCNC CD274 CDC73 CDH1 CDH10 CDH11 CDK12 CDKN1B CDKN2A CDKN2C CDX2 CEBPA CHD2 CHEK2 CIC CIITA CLTC CLTCL1 CNBP

CNOT3 CPEB3 CREB3L1 CREBBP CTCF CUL3 CYLD DAXX DDX10 DDX3X DICER1 DNM2 DROSHA EBF1 EED EIF3E ELF3 ELL EP300 EPS15 ERCC2 ERCC3 ERCC4 ERCC5 ETNK1 ETV6 EXT1 EXT2 FANCA FANCC FANCD2

FANCE FANCF FANCG FAS FAT1 FAT4 FBLN2 FBX011 FBXW7 FEN1 FH FHIT FLCN FUBP1 FUS GATA1 GATA3 GPC5 GRIN2A HNF1A ID3 IGF2BP2 IKZF1 KAT6B KDM5C KDM6A KEAP1 KLF6 KMT2C KMT2D KNL1

LARP4B LATS1 LATS2 LEPROTL1 LRIG3 LRP1B LZTR1 MAP3K1 MAX MEN1 MGMT MLF1 MLH1 MSH2 MSH6 MUTYH MYH9 N4BP2 NAB2 NBN NCOA4 NCOR1 NCOR2 NDRG1 NF1 NF2 NFKBIE NOTCH1 NOTCH2 NRG1 NTHL1

PALB2 PATZ1 PAX5 PBRM1 PER1 PHF6 PHOX2B PIK3R1 PML PMS2 POLD1 POLE POLG POT1 PPARG PPP6C PRDM1 PRDM2 PRF1 PTCH1 PTEN PTPN13 PTPN6 PTPRB PTPRC PTPRD PTPRK PTPRT RAD17 RAD51B RANBP2

RB1 RBM10 RFWD3 RHOH RMI2 RNF43 ROBO2 RPL10 RPL22 RPL5 RSPO2 RUNX1 SBDS SDHA SDHAF2 **SDHB** SDHC SDHD SETD1B SETD2 SFPQ SFRP4 SH2B3 SIRPA SLC34A2 SMAD2 SMAD3 SMAD4 SMARCA4 SMARCB1 SMARCD1

SMARCE1
SMC1A
SOCS1
SOX21
SOX9
SPEN
STAG1
STAG2
STK11
SUFU
TET2
TGFBR2
TMEM127
TNFAIP3
TNFRSF14
TP53
TPM3
TRAF7
TRIM33
TSC1
TSC2
USP44
VHL
WIF1
WNK2
WRN
WT1
XPA
XPC
YWHAE
ZBTB16

ZFHX3 ZMYM3 ZNF331 ZNRF3 ZRSR2

Table S4. Overlapped pathways dysregulation in aging and cancer

Callular processos	The percentage of dysregulated cellular processes[1]														
Cellular processes	Adrenal gland Br	east	Colon sigmoid	Colon sigmoid Uterus		Esophagus Stomach Liver			Lung Ovary		Prostate	Average			
Upregulation in aging & cancer	2.5	11.5	5.1	1.7	6.6	4.1	0.4	11.3	3.3	0.9	5.4		4.8		
Downregulation in aging & cancer	12.6	10.9	21.6	17.3	26.2	0.5	9.6	9.9	12	0.9	10.3		12		
Upregulation in cancer & downregulation in aging	9.2	8.1	21.7	16.7	41.3	23.6	6.2	24.1	41.6	4.5	7		18.5		
Dowregulation in cancer & upregulation in aging	3.3	13.7	11.9	1	6.5	0.7	1.7	30.8	4.1	0.2	21.7		8.7		
TOTAL	27.6	44.2	60.3	36.7	80.6	28.9	17.9	76.1	61	6.5	44.4		44		

[1] The percentage of dysregulated pathways in all cellular process overlapped in aging and cancer in corresponding tissues.

Table S5. Overlapped unidirectionally dysregulated pathways in aging and cancer

Pathways[1]	Upstream signaling pathways	Main cellular processes	Unidirectional dysregulation in aging and cancer	GTEx tissues	iPANDA score (aging)	Cancer types	iPANDA score (cancer)
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Adrenal gland	0.0102	Adrenocortical carcinoma	0.042
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Breast	0.0527	Breast carcinoma	0.1831
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Lung	0.0313	Lung cancer	0.139
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Pancreas	0.0174	Pancreatic carcinoma	0.1421
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Prostate	0.0347	Prostate adenocarcinoma	0.077
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Stomach	0.0191	Gastric carcinoma	0.1638
Cellular Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Colon sigmoid	0.0112	Colorectal carcinoma	0.0715
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Stomach	0.0506	Gastric carcinoma	0.1495
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Lung	0.0767	Lung cancer	0.0629
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Pancreas	0.051	Pancreatic carcinoma	0.1884
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Prostate	0.0617	Prostate adenocarcinoma	0.0374
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Breast	0.0761	Breast carcinoma	0.1067
Oncogene Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Colon sigmoid	0.0587	Colorectal carcinoma	0.083
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Breast	0.0446	Breast carcinoma	0.2781
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Colon sigmoid	0.0272	Colorectal carcinoma	0.0526
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Lung	0.051	Lung cancer	0.1834
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Pancreas	0.0277	Pancreatic carcinoma	0.1415
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Prostate	0.0419	Prostate adenocarcinoma	0.0938
Oxidative Stress Induced Senescence	Cellular Senescence	Cellular response to external stimuli	Upregulation	Stomach	0.0343	Gastric carcinoma	0.1726
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Adrenal gland	-0.0358	Adrenocortical carcinoma	-0.0311
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Breast	-0.0313	Breast carcinoma	-0.2577
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Colon sigmoid	-0.0108	Colorectal carcinoma	-0.1508
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Esophagus	-0.0785	Esophageal carcinoma	-0.0703
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Liver	-0.0209	Hepatocellular carcinoma	-0.0156
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Ovary	-0.1015	Ovarian carcinoma	-0.0557
Adenylate cyclase inhibitory pathway	GPCR downstream signalling	Signal transduction	Downregulation	Uterus	-0.1387	Endometrial cancer	-0.3542
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Adrenal gland	-0.0259	Adrenocortical carcinoma	-0.0384
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Breast	-0.0225	Breast carcinoma	-0.1996
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Colon sigmoid	-0.0125	Colorectal carcinoma	-0.1505
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Esophagus	-0.0907	Esophageal carcinoma	-0.0604
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Liver	-0.0145	Hepatocellular carcinoma	-0.0472
G-protein mediated events	GPCR downstream signalling	Signal transduction	Downregulation	Ovary	-0.087	Ovarian carcinoma	-0.056
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Colon sigmoid	-0.0399	Colorectal carcinoma	-0.0389
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Esophagus	-0.2263	Esophageal carcinoma	-0.2972
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Lung	-0.0635	Lung cancer	-0.1342
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Ovary	-0.06	Ovarian carcinoma	-0.0135
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Prostate	-0.0481	Prostate adenocarcinoma	-0.1793
GAB1 signalosome	Signaling by EGFR	Signal transduction	Downregulation	Uterus	-0.2109	Endometrial cancer	-0.0737
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Breast	-0.0132	Breast carcinoma	-0.0102
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Colon sigmoid	-0.0405	Colorectal carcinoma	-0.0972
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Esophagus	-0.09	Esophageal carcinoma	-0.0466
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Liver	-0.0105	Hepatocellular carcinoma	-0.0521
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Lung	-0.0386	Lung cancer	-0.1614
MAP2K and MAPK activation	MAPK1/MAPK3 signaling	Signal transduction	Downregulation	Prostate	-0.057	Prostate adenocarcinoma	-0.0723

[1] Reactome pathways that are dysregulated in a unidirectional manner in more than 5 types of cancer (i.e., 50%) and their corresponding healthy GTEx tissues

Table S6. Top 100 AI-derived common high confidence and novel cancer targets	

					Ranking		_			Aging				Cancer		-					Aging-association	_		
argets	Protein family	Clinical	Novelty[1]		Number o	r .	Number of aging	Hallmarks of aging			Number of	Number of cancer	Number of	Number of	Number of	Therapeutic approach for	Reported in database;	Observed effects on longevity[5]		nvolved in	Group 1: Evidence in extending lifespan, dual- purpose (same direction of therepeutic inhibition or activation) Group 2: Evidence in extending lifespan, not dual-	GenAge /	Remarks	P. farmer
irgeis	r roteni tanniy	trial status	Novenyjij	Overall rank[2]	cancers (ranked as t 100)	Avera op e rani		Tanna Ki Gi Aging	Number of dysregulation	upregulatio n	Number of downregulatio n	hallmarks[4]	Number of dysregulation	n n n	downregulatie n	cancer treatment[6]	Results	Oncerved enects on nungerity[5]	approach for tary	get wheel[7]	purpose (opposite direction of therepeutic inhibition or activistion) Group 3: Evidence in shortening lifespan only non 4: Unexploring role in regulating lifespan NA: Excluded in target wheel (due to lack of aging hallmarks or less than 7 tissues dysregulated GTEx tissues during aging)	Geroprotectors / SynergyAge)	KISHIRK	Refreices
KTI	AGC kinase	Yes	нс	1	11	113	12	A Reno uncercentar communications, Cellula senescence, Deregulated nutrient signaling, Epigenetics shift, Extracellular matrix stifflerse, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Retrotranspositions, Stee	11	1	10	10	8	5	3	Antagonism	Reported; Lifespan extension	Anti-Longevity: Debtion mutation (da-1 mg/06) increased lifespan in <i>C. elogant</i> . Debtion mutation (da-1 ed-3) increased lifespan Debtion mutation (da-2 ed-39) increased lifespan in <i>C. elogant</i> . Heterogeneous knockout mutatist (da1) increased lifespan in mice		Yes	Group 1	SynergyAge,GenAge	AKTI as a therapeutic target (astagonia) for cancer.	PMID: 239354 PMID: 360867 PMID: 1524013 PMID: 1524013 PMID: 1824185 PMID: 278648 PMID: 163918 PMID: 2341522 PMID: 2180328 PMID: 2180328 PMID: 2180328 PMID: 2341522 PMID: 2341522 PMID: 2341522
SR1	Nuclear recepto	r Yes	нс	2	11	22.4	5	Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation, Stem cell exhaustion	18	12	6	5	10	1	9	Antagonism*	Reported; Lifespan extension	Pro-Longevity: 17-a-estradiol (ESR 1 agonist) extended lifespan in mice ic, preferentially in makes. Beta-Estradiol (ESR 1 agonist) induced the ESR 1 translocation to the cell membrane, and was shown to increase lifespan in C cleggar. Estradiol (ESR 1 agonist) extended lifespan significantly in C. cleggars and mice.	Agonism	Yes	Group 2	rugAge, Geroprotector	Antagonisi or agonisi for cancer. Fulvestrant and amoviène are used for breast cancer treatment. For intance, fulvestrant, TSR li inhibitor, used to treat IR+ breast cancer that may also be IER22, while amovién is both an antagonist and an agonist of the estrogen receptor.	PMID: 242455 PMID: 179286 PMID: 904531 PMID: 241346 PMID: 241346 PMID: 273122 PMID: 337232 PMID: 337883
.К1	Protein kinase	Yes	нс	3	11	29.5	4	Cellular senescence, Genomic instability, Impaired proteostasis, Inflammation	13	4	9	2	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. PLK1 is involved in cell cycle regulation and DNA checkpoint during healthy aging. PLK1 promotes autophagy. polo loss-of-function increased lifespan of atheimmer-like Drosophila . Antagonist for cancer.	PMID: 281027 PMID: 265977
MTI I	fethyltransferas	se Yes	HC	4	11	30.4	2	Epigenetic shift, Genomi instability Cetutar senescence, Extracellular matrix	c 15	1	14	I	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		DNMT1 maintaine around the tank to tank to DNAT methylation affects and any and promotes age-related DNA methylation affects and/sy aging and promotes age-related description affects and any and any and any and any and No difference in longevicity any product between Dmm1-deficient mice and normal controls.	PMID: 227043 PMID: 16510
DK1	CMGC kinase	Yes	нс	5	11	31.2	6	Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction, Stem cell	13	4	9	3	11	11	0	Antagonism	Reported; Lifespan extension	Anti-Longevity: cdk-1 RNAi increased lifespan by 43% in C. elegans.	Antagonism	Yes	Group 1		Antagonist for cancer. CDK I is involved in cell cycle regulation during healthy aging	PMID: 27668
EK1	Protein kinase	Yes	нс	6		31.6	3	Cellular senescence, Epigenetic shift, Genomi instability Azereed interceutar communications, Cellula senescence, Deregulated	r	6	12	2	10	10	0	Antagonism	Reported; Lifespan extension	$\begin{array}{llllllllllllllllllllllllllllllllllll$	Agonism	Yes	Group 2	GenAge	Antagonist for cancer. CHEK1 is involved in DNA damage response and cell cycle checkpoint response during bealthy aging	PMID: 27668 PMID: 16741
GFR	Receptor kinase	e Yes	HC	7	11	35.6	10	nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Stem cell exhaustion, Telomere	17	0	17	7	8	2	6	Antagonism	Reported; Lifespan extension	Pro-Longevity: let-23 (gain-of-function) mutants lifespan increased by 29%, while let-23 (loss-of-function) mutants lifespan decreased by 19% in <i>C. elegans</i> .	Agonism	Yes	Group 2	GenAge	Antagonist for some cancers but IGGR ehabitists neutist is skin aging and age-related decline. IGGR hisbitists was shown to moleculur alterations in kerntinosytes, ikely outstheining to the observed skin aging IGGR activation promoting extended healthspan, while EGGR macrination associated with age-related decline.	PMID: 271650 PMID: 20497
RCA1	Acyltransferase	2 No	HC	8	11	36.4	6	Altered intercellular communications, Cellula senescence, Epigenetic shift, Genomic instability Impaired protoostasis,	r , 19	3	16	7	10	10	0	Antagonism	Reported; Reduced lifespan onl	Pro-Longevity: h Heterogeneous BRCA1 mutant lifespan was decreased in mice.	NA	Yes	Group 3	GenAge	Tumor suppressor gene	PMID: 17420
EK2	Protein kinase	Yes	HC	9	11	37.9	3	Stem cell exhaustion Cellular senescence, Genomic instability, Impaired proteostasis Centuar senescence, Deregulated nutrient signaling Extracellular	15	14	1	2	9	9	0	Antagonism	Reported; Lifespan extension	Anti-Longevity- * Lifespan of Brca1A11/A11Chk2-/- mice longer than Brca1A11/A11p53+/- in mice.	Antagonism	Yes	Group 1	GenAge	Tumor suppressor gene CHEK2 inhibitors were invesigated in multiple cancers (max p2 completed, NCT03414047)	PMID: 16675
DR	Receptor kinase	e Yes	HC	10		42.7	8	signaling, Extracellular matrix stiffness, Genomi instability, Impaired proteostasis, Mitochondrial dysfunction, Stern cell exhaustion, Telomere	12	3	9	7	9	2	7	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		KDR antagonists such as Ramacimumb, Caboxantinb approved for cancer treatment but our data showed KDR downtregalation in cancers. KDR may be needed for normal angiogenesis, to ensure developing or healing tissues receive an adequate supply of nutrients.	
MP2	Peptidase	Yes	HC	11	11	44.5	6	Extraceiniar matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial	13	11	2	5	9	4	5	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Matrix metalloproteinases are involved in cancer invasion and metastasis - advanced stage of cancer. Aging is associated with increased matrix metalloproteinase-2 activity in the human aotta MMP2 was considered as classical sensecance-associated secretory phenotype (IASP).	PMID: 15831
ARCA4	Hydrolase	No	HC	12	11	49.7	5	Altered intercellular communications, Cellula senescence, Epigenetic shift, Genomic instability Stem cell exhaustion Anerea intercentuar	27	2	25	0	11	10	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Tumor suppressor gene	
	CMGC kinase CMGC kinase		нс	13	10	16.5 22.9		communications, Deregulated nutrient signaling, Epigenetic shift Extracellular matrix	17	2	15	6	10	10	0	-		Pro-Longevity: Overexpresision of CycD/Cdk4 in Drosophila increased lifespan. Anti-Longevity:	Agonism	Yes	Group 2		Antagonist for cancer. CDK4 is involved in cell cycle regulation during healthy aging	PMID: 26219
n6.2	C MUC knase	Yes	HC	14	10	22.9	2	Genomic instability Attered intercentuar communications, Cellular senescence, Deregulated nutrient signaling	7 1	4	3	4	10	10	0	Antagonism	reported; Litespan extension	cdk-2 RNAi increased lifespan by 28% in C. elegans . Anti-Longevity: Overexpression hPARP1 (double knock-in) significantly decreased lifespan in mice.	Antagonism	Yes	Group 1			PMID: 27668
RP1 G	lycosyltransfera	ise Yes	HC	15	10	24.6	10	Epigenetic shift, Extracellular matrix staffness, Genomic instability, Inflammation Mitochondrial dysfunction, Stem cell exhaustion, Telomere Cenumi sensecence, Genomic instability.	32	1	31	3	11	10	I	Antagonism	Reported; Lifespan extension	Mutation, RNA i and PARP inhibitors (AZD2381/ABT-888) extended lifespan by 29%, 20%, 15-23% in C. elegans, respectively. pme-l mutated increased lifespan in C. elegans. Muscle PARP1 inhibition extends lifespan in Drosophila	Antagonism	Yes	Group 1	GenAge	Antagonist for cancer. PARP1 is involved in base excision repair during healthy aging.	PMID: 20561 PMID: 23870 PMID: 31878 PMID: 36947
JRKA	Protein kinase	Yes	HC	16	10	27.0	6	Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Stem cell	18	2	16	0	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. AURKA is involved in cell cycle regulation during healthy aging	

VEGFA	A. Gn	rowth factor	Yes	нс	17	10	29.3	8	Altered intercellular communications, Cellular sensecence, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation, Telomere attrition Anerece mercenuar	13	9	4	5	11	10	ı	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. Countencing age-techted VECF signifing noufficiency promotes healthy aging and extends lifespan.	PMID:34326210
PPARG	i Nue	clear receptor	Yes	HC	18	10	30.1	9	communications, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomie instability, Inflammation, Mitochondrial dysfunction, Stem cell exhaustion, Telomere	13	1	12	3	8	2	6	Agonism	Reported; Lifespan extension	Pro-Longervity: Ala/Ala Kencke in Hispen arcrassed by 17%, and bypomorphic mutant decroses lifespan by 11% in mice Bearflorate againing PPARG extended lifespan significantly is C. elegony. Hypomorphic Pargg12 backaet decrossed lifespan in mice.	Agonism	Yes	Group 1	ge,GenAge,Geroprotec	Типког наррговоо gene; Адания for cancer Адана очетсяреенного от сляжая и па не отван от писе темитеа и	PMID: 19117549, PMID: 23603800, PMID: 19997628
GSK3B	3 CN	MGC kinase	Yes	нс	19	10	30.9	9	Ahered intercellular communications, Cellular sensescence, Deregulated nutrient signaling, Epigenetic skift, Genomic instability, Impaired protocotasis, Inflammation, Mitochondriai dysfunction, Stern cell exhaustion	33	0	33	7	9	9	0	Antagonism	Reported; Lifespan extension	Anti-Longevity- sg (GKKI) (EVA: increased the lifegum in <i>Drosophia</i> . Induced Sector (Sectored Sectored Sectored Sectored Sectored Sectored Sectored Sectored Sectored Sectored Efficiency processing Sectored Sectored Efficiency processing Sectored Sectored Sectored Sectored Sectored Sectored Sectored Sectored Sectored	Antagonism	Yes	Group 1	JrugAge,Geroprotector	nerodogeneration. Key modators of seconce signaling under a jo sind p53 physically instructs with GSR2[k] and cit as in patient exhibiting. Lew dow follman major promoted linegrity in homan and C. Lishum chhords anzapaning GSR3 Bestradd Briegan significantly in C. degress and Drosophile. Therapente surgeting of GSR3 by nicedoos thilam later is the decremoid senseconce significantly discover and the second in the second second second second second second second in the second second second second second second second edges and the second second second second second second in the second second second second second second second second edges are coold and centered likepan in and gale-3 (sec2071) mutant relations in filting matalesis compared with the pC e. Coopers. The second second sec	PMID: 2768360, PMID: 1795960, PMID: 21301855, PMID: 24398558, PMID: 24398558, PMID: 31166234
MTOR	: Pro	otein kinase	Yes	нс	20	10	33.4	12	Altered metercellular communications, Cellular senescence, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffices, Genomic instability, Impaired protostasis, Inflummation, Mitochondrial dysfunction, Retrotranspositions, Stem	32	0	32	6	8	6	2	Antagonism	Reported; Lifespan extension	Anti-Lengenty: Its recondverses, TGG deficiency more than doubled the lifeopan. TGG diaruption is <i>Drosophila</i> table extended lifeopan. Hypomorphic mutation science lifeopan by 20% in Knockdown of TOR mersuse the longenity of de- 2mutation is <i>C. elagarst</i> . MTOR lambher, rapmynie extended lifeopan and delogs operation in the longenity in drosophila and muscle longenity in drosophila and muscle longenity in drosophila and muscle.	Antagonism	Yes	Group 1		MTOR inhibitor, eventimes (gastrointestinal or lang origin with unresetable, locally advanced or metatatic disease), temisiolinus (Renal cell carcinom) were approved drug for cancer tentment.	PMID: 1727769, PMID: 1466850, PMID: 15180745, PMID: 2545024, PMID: 22607469, PMID: 22017699, PMID: 2244993, PMID: 19387880, PMID: 24469289
PIK3CA	A Non-j	-protein kinase	e Yes	нс	21	10	33.6	9	Altered intercellular communications, Cellular senescence, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inpaired proteostasis, Mitochondrial dysfunction, Telomere attrition	19	3	16	9	6	3	3	Antagonism		age-1 mutants lifegan moremel by 60% in C- ciegan. age-1 (hts64) mutants lifegan increased by 40- 10% ACAA) increased lifegan increased by 10% in C- age-1(k2AA) increased lifegan increased by 100% in G-ciegans. age-1(hts64) mutants lifegan increased by 100% in C-ciegans. age-1(hts64) mutants (-ciegans were house-fived by age-1(hts64) mutants (-ciegans were house-fived by age-1(hts64) mutants (-ciegans were house-fived by significant a C- ciegans.	Antagonism	Yes	Gitoup 1	ige, GenAge, SynergyA	Suppressing the activity of the p11 Bulpha isoform of PIKSCA preserved cardine function and prevented cardine sping in more. MOR0 is advancement effective of PIA. Sedente material spin and set of the set of the set of the Begun in Droughtild. PL3-kane p11 Gl4bab submit hibbits was westigned edugs in various clinical trials for cancer treatment.	PMID: 2254423, PMID: 2252631, PMID: 758764, PMID: 758764, PMID: 1958008, PMID: 1958009, PMID: 1968097, PMID: 19622007, PMID: 10622007, PMID: 10520072
ERBB2	2 Rec	ceptor kinase	Yes	HC	22	10	35.5	3	Cellular senescence, Deregulated nutrient signaling, Impaired proteostasis	17	6	11	6	10	6	4	Antagonism	Reported; Lifespan extension	Pro-Longevity: Let-23 mutant (relatcion-of-fanction) survive less robustly in middle aduthhood than matched wild type controls (19% decrease of machian lifespan, 8% decrease of maximum lifespan) in <i>C. elegans</i> . Let-23 mutants (gain-of-function) survive more robustly in middle aduthhood (29% increase of median lifespan, 9% increase of maximum lifespan) in <i>C. elegans</i> .	Agonism	Yes	Group 2	GenAge	Antagonisi for encore but ERBE2 signaling is important for bealth. ERBE2 signaling in the heart is essential for the prevention of dilated candionyapathy, and ERBE2 is necessari for eligodentinocytes, specialized glial cells, myelunte CNS acoust. ERBE2 is healthy driver.	PMID: 35370556, PMID: 1474944, PMID: 20497132, neg kel ac uk/index php
MET	Rec	ceptor kinase	Yes	HC	23	10	39.3	3	Mitochondrial dysfunction, Telomere Extraceinular matrix	19	3	16	8	10	8	2	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-	Antagonist for cancer. MET is a target of multiple approved drugs such as cabozantinib, crizotinib and brigatinib for cancer	PMID: 28677234
MMP9) I	Peptidase	Yes	нс	24	10	39.9	6	stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial	3	1	2	7	9	9	0	Antagonism	Not reported	No evidence	NA	No			< 7 tissues (out of 47) dysregulated during aging Antagonist for cancer. MMP-9 short interfering RNA induced sensescence and MMP9 is one of CellAge Database of Cell Sensescence Genes	PMID: 17510426, https://genomics.senescence.info/
Ш.6	Ŀ	Interleukin	Yes	HC	25	10	53.0	7	Altered intercellular communications, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation, Stem cell exhaustion Altered intercellular	3	2	1	6	6	2	4	Antagonism	Not reported	No evidence	NA	No			< 7 tissues (out of 37) dynegolated during aging IL6 attagonests such a Siliccianal approved for immute system doctors and is overrogalized in cuerces. Pro-inflummatory cytakine IL-6 a commonly present in the the sensecreto-associated secretory phonolyte (SAS). Interleakin-6 knockout inhibits ensectioned brote bros sense methods in high-fad dis-induced brote bros	PMID: 33679606
CDK6	CN	MGC kinase	Yes	HC	26	9	27.6	4	communications, Cellular senescence, Extracellular matrix stiffness, Stem cell exhaustion	15	3	12	4	7	5	2	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. CDK6 is involved in cell cycle regulation during healthy aging	
AR	Nuc	clear receptor	Yes	нс	27	9	31.9	6	extantistion Altered intercellular communications, Deregulated nutrino signaling. Pignencis shift, Extracellular matrix stiffness, Genomic instability, Inflammation	23	6	17	2	8	1	7	nism / Antagon	Reported; Lifespan extension	Pro-Longevity: Danazol agonising AR & PGR extended lifespan in <i>C. elegans</i> .	Agonism	Yes	Group 2)rugAge,Geroprotector	Pagnetic induced intellin statisticity and impaired glocose characte- were exe as Al-bacedoratine with sharing age: Aging a Ak-tanekont mice displayed accelerated weight gain, bypersultaintian, and bypergylerenian, and to act Ad construction increased trigbyeredire constant in a heekad muncle and here. Detracy cohore territorio, which refatts agrees and extends lideput, serverse has or AK expression and restore they cohore territorio, which refatts agrees of postst caracter- ance and the structure of the structure of postst caracter. Our data howed and Ad constructivities of scareer. Our data howed and Ad constructivities of scareer.	PMID: 19919793, PMID: 1986927, PMID: 8706808, PMID: 24134630
IGF1	Gn	rowth factor	Yes	нс	28	9	32.0	12	Altered intercellular communications, Cellular termino, C. Calland Foreiner, C. Schlandel Foreiner, S. Status, S. Status, Foreiner, S. Status, S. Status, Inflammation, Macchoodraid dysfunction, Sem cell exhaustion, Telonare attration	15	б	9	8	8	I	7	Antagonism*	Reported; Lifespan extension	Anti-Longovity: Congamillar (FG-1-deficient time were increased with Hergen Hypotonybic materia increased (Fyptonophic materia increased) C. elgour Histopia octamina fields increased for every present and increased FG-1 cardia-ageodity Pro-kongevity: FG-1 cardia-ageodity (FG-1 cardia-ageodity) FG-1 cardia-ageodity (FG-1 cardia-ageodity) (FG-1	nism / Antagon	Yes	Group 2	GenAge	KGT inhibitors such as xenturannah, dasigitamah were investigated for cancer transment in clinical traits. Insulin resistance is increased with aging. More lacking KGT in the been hare shown to indiper shanched rainals sensitivity and glucose the structure of the structure of the structure of the 10% increases in Hiegan. However, KGT-1 canhae-specific overcupression increased Blogana minic: — Profector KGT-1 on longevity may be insue-specific.	PMID: 2179924, PMID: 2441499, PMID: 2441499, PMID: 247364, PMID: 2797811, PMID: 20197811, PMID: 20198554

NR3C1	Nuclear receptor	Yes	нс	29	9	34.8	4	Altered intercellular communications, Extracellular matrix stiffness, Genomic instability, Mitochondrial dysfunction Auereu nuevcenan communications Cellular	14	4	10	0	10	2	8	Agonism	Not reported	No evidence	NA	Yes	Group 4		NR2C1 gooint was investigated for cancer treatment is distical triads. Mice with support NR2C1 functions advanced below sourced durings induces of cognitive impairment. Cyptoteneous acetate inhibiting AR, RGR & NR2C1 (approved for human use presented lifespan is c. c. c. c. gasar. Decamethosones, NR2C1 associatis, has been used for cancer treatment. MPAPI (GRX1) magnitis such as discertioned for cancer treatment.	PMID: 33684964, PMID: 24134630
МАРКЗ	CMGC kinase	Yes	HC	30	9	35.4	7	communications, Cenuar senescence, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction, Stem cell exhaustion, Telomere Akered intercellular	19	8	11	9	10	2	8	Antagonism* Re	eported; Reduced lifespan only	Pro-Longevity: RNA interference of mpk-1 resulted in a decrease in lifespan in <i>C. elegans</i> .	NA	Yes	Group 3	GenAge	MAPK-1 (LKA) Jalingsinst site in a surfame and tenuiterub were investignale for cancer treatment. Age-associated selective impairment in the MAPK signaling pathways in the ago brain. Lifebong calorie restriction completely prevented the age-related decrease in base brain ERK activity and dimnished the age-related reduction of p38 MAPK activity.	PMID: 10647963, PMID: 20624915, PMID: 18059442
CASP3	Peptidase	Yes	нс	31	9	37.7	6	A lered intercellular communications, Cellular senescence, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction	18	0	18	8	7	7	0	Antagonism I	Reported; Lifespan extension	Anti-Longevity: * RNA interference (ced-3) in adulthood resulted in a 19% increase in mean lifespan in <i>C elegans</i> .	Antagonism	Yes	Group 1	GenAge	Tumor suppressor gene	PMID: 17411345
TGFB1	Growth factor	Yes	нс	32	9	39.1	7	Ahered intercellular communications, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation, Stem cell exhaustion	21	18	3	7	9	5	4	Antagonism I	Reported; Lifespan extension	Anti-Longevity; daw (RNAi) increased lifespan by 35% in <i>Drosophila</i> . Muscle specific daw (RNAi) increased lifespan hy 11% while fit specific daw (RNAi) decreased lifespan (PMID: 24244197).	Antagonism	Yes	Group 1	GenAge	TGFB1 inhibitor or binding agent was investigated for cancer restance in trials. Upregulation of TGF4 glagado controls to coll degeneration, tissue fibronis, inflammation, decreased regeneration capacity, and metabolic malfunction.	PMID: 31638394
NOTCHI	Receptor	Yes	нс	33	9	43.7	5	Akered intercellular communications, Extracellular matrix stiffness, Genomic instability, Inflammation, Stem cell exhaustion	16	6	10	6	9	4	5	Antagonism I	Reported; Lifespan extension	Anti-Longevity: * glp-1(q158) mutants lifespan increased by 30% in <i>C. elegans</i> . glp-1 (RNAi) increased lifespan by 33% in <i>C.</i> <i>elegans</i> . A temperature-sensitive glp-1 mutant, which lacks a gemline, is long-lived at the non-permissive temperature in <i>C. elegans</i> .	Antagonism	Yes	Group 1	GenAge,SynergyAge	Tumor suppressor gene, NOTCH1 inhibury anthody was investigated in metastatic coherectal cancer (p1 completed, NCT03031691)	PMID: 22291607, PMID: 26378790, PMID: 21906946
KRAS	Hydrolase	Yes	нс	34	9	44.9	3	Altered intercellular communications, Genomic instability, Mitochondrial dysfunction	20	1	19	9	9	7	2	Antagonism	Not reported	No evidence Anti-Longevity:	NA	Yes	Group 4		Antagonist for cancer. KRAS inhibitor such as solorasib was approved for cancer Genetic inhibition of Ras was found to extend lifespan. Aduk-onset administration of the drug tramentim inhibiting MAP2K1 and MAP2K2, a highly specific inhibitor of Ras-Erk-ErS signaling, extended lifespan in <i>Drosophila</i> .	PMID: 29276789, PMID: 26119340
HDAC1	Hydrolase	Yes	HC	35	9	47.6	7	Ahered intercellular communications, Cellular senscence, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation, Stem cell exhaustion	24	6	18	2	10	9	1	Antagonism I	Reported; Lifespan extension	Hypomorphic mutation increased lifespan by 33- 52% in <i>Drosophila</i> . Heterogeneous mutation increased male lifespan by 41 - 47%, while no charge in median of female lifespan. Rpd3 activity in reduced by colories extriction, which causes the increase in SiZ activity and lifespan extremision in <i>Drosopary</i> ; Gaino-of-function (rdZ)23/241 doi:10.2108/	Antagonism	Yes	Group 1	GenAge,SynergyAge	Astagovist for carner HDAC1 inhibitory, vorinsent and runidepsin were approved for the transmersion of contaneous. Teell hypothema Inactiviting historic description HDA protocols longerity by mobilizing trehalose metabolism.	PMID: 12459580, PMID: 33790287, PMID: 10512855, PMID: 15520384
VDR	Nuclear receptor	Yes	HC	36	9	48.0	1	Genomic instability	14	1	13	0	7	6	1	Agonism* I	Reported; Lifespan extension	increased lifespan significantly while loss-of- function (th6/th4/11) daf-12 decreased lifespan significantly. Double mutation daf-2 (IGF-1) and daf-12 increased lifespan with a syneepsitic effect but single null mutation daf-12 shorten lifespan. Deletion nhr-8(ok186) extended lifespan in C. elegans.	Agonism	Yes	Group 1	GenAge,SynergyAge	VDR agonists were investigational for cancer. VDR knockout mice showed several aging telled phenotypes, including poorer survival.	PMID: 16626392, PMID: 7789761, PMID: 79500727, PMID: 24655420, PMID: 25209682, PMID: 30125273
TERT	Transferase	Yes	нс	37	9	54.1	8	Anerea metrcenuar communications, Cellular senescence, Genomic instability, Impaired protoestasis, Mitochondrial dysfunction, Retrotranspositions, Stem cell exhaustion, Felomere	3	1	2	6	7	6	ı	Antagonism I	Reported; Lifespan extension	However, two other studied showed dekion nhe- Pro-Longery's: TERT overception (K-S-mTeth) increased lifespin by 10% in mic. Tet of the strength of the strength of the lifespin by 10% in mic. Tet overcepting in the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the lifespin by 10% in the strength of the strength of the strength of the lifespin by 10% in the strength of the strength of the strength of the lifespin by 10% in the strength of the strength of the strength of the lifespin by 10% in the strength of the st	Agonism	No	-	GenAge	4.7 Sinues (not of 47) dynamical during uping Overcopression of teleneouse can shifted aging but at the expense of increased lumorigeneous	PMID: 17876321, PMID: 23211840, PMID: 15688016 PMID: 15688016 PMID: 21113150
TLR4	Receptor	Yes	нс	38	8	25.3	8	Akered intercellular communications, Deregalated nutrient signaling. Fpigenetics shift, Extracellular matrix shifthess, Genomic instability, Inflarumation, Retrotranspositions, Stem cell exhaustion	16	10	6	6	8	3	5	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		Like is an important ration Recognition Receptor (price), when activates both mates and adprive numme cells. In actionical leads in influminatory systelic productions which is responsible for advinting the matter immune system. The statistical production (management) and the statistical behaviory but reduced production (management) The Toi-Rie receptor 4 (TLR4) signific prices and the prices protons of provide the statistical differentiation, and of providementory volvide products, my cloud differentiation, and Antagenite for encare, one of that showed NLW1 sprenglation in	PMID: 32508811, PMID: 30336978
NME1	Unclassified kinase	e No	нс	39	8	39.4	2	Genomic instability, Impaired proteostasis	8	0	8	0	10	10	0	Antagonism I	Reported; Lifespan extension	Anti-Longevity: * ndk-1 (RNAi) increased lifespan >5% in C. elegans .	Antagonism	Yes	Group 1	GenAge	Hungmun in teach, a bot cannot be write a spregaration in However, NME1 is considered as (1) metastasis suppressor and (2) metastasis promotor. NME1 depletion resulted in significantly more npid migration of metroblustoma cells NME1 protects against neurotoxis, o Synachein- and LRRK2. induced neurite degeneration is cell models of parkinsor's discuss.	PMID: 26620638, PMID: 30026594, PMID: 34623600, PMID: 28991262
FGF2	Growth factor	Yes	нс	40	8	43.9	7	Altered intercellular communications, Cellular senescence, Deregulated nutrient signaling, Extracellular matrix stiffness, Inflammation, Stem cell exhaustion, Telomere attrition	14	11	3	6	10	I	9	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		FGF2 is a major pro-angiogenic factor during tumor angiogeneix but FGF2 (or bFGF) is neuroprotective for healthy aging. It can improve motor function troovery, increase tyronic hydroxylate possible neurona neurotransmitters in the brain of a rat major guide of Parkinson's disease.	PMID: 30274251
CXCR4	GPCR	Yes	нс	41	8	44.0	5	Extracellular matrix stiffness, Genomic instability, Impaired protocutasis, Inflammation, Stem cell exhaustion	23	22	1	6	9	7	2	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. CXCR4 overexpression contributes to tumor growth, progression and metastasis. CXCR4 gene deletion in young metescholymalisticm cells accelerates an aging phenotype including increased production of reactive oxygen species, DNA damage, sensectore, and reduced proliferation. In constrat, CXC1.12.CXCR4 promotes inflummation. Targering CXCR4 for antiaging may be sublift for aged adults only.	PMID: 26848769, PMID: 32418119
FASN	Acyltransferase	Yes	нс	42	8	48.0	3	Deregulated nutrient signaling, Epigenetic shift, Inflammation	18	1	17	1	7	6	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer, FANS inhibitor prevented the initiation of sensecence induction in bematopoicitic store cells and reduced the effect of the activation of sensecence on different age-associated diseases. DEHPDEP (increasing fasn-1 expression, and affecting other lipid metabolic games) treated <i>C. dogatas</i> Infospan decreased.	PMID: 30962418, PMID: 29020644
PDGFRB	Receptor kinase	Yes	HC	43	8	48.4	6	Cellular senescence, Deregulated nutrient signaling, Extracellular matrix stiffness, Genomic instability, Impaired protecostasis, Stem cell exhaustion	18	12	6	6	10	5	5	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-	Antagenist for cancer. PDGFR & signaling in the cardiomyceyte may regulate angiogenesis in the hart in repose to load-induced traves through several different mechanisms. Intarinib metyicat holing (FOGRR AR, ARL), KAT, BCR reduced lifespan in C. abgont.	PMID: 20071776, PMID: 3201088

MDM2	Acy	ltransferase	Yes	HC	44	8	64.0	3	Cellular senescence, Genomic instability, Impaired proteostasis	13	9	4	7	7	6	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4	·	Antagonist for cancer, encopyote in Min2 in cancer MMM is a negative regulator of p53, a tunnor-appressor gote. Dominant-appears were not or Dominal to many strategiest p53 as shaft that supplet, anguating MMM any special strategiest p54 as a shaft performer, statish noiscite MMM any appears larger the streetened to perform any strategiest participation of the streetened baseness overexpression of wild key pep3 in abid the abi- shortned Holpenn Hendes by the streeted Hopen in males. MDM anguastic Min2 and the streetened streetened combined immandeficients.	PMID: 28402501, PMID: 1630358, PMID: 1795412, PMID: 1795424
TGFBR:	? Rec	eptor kinase	No	HC	45	7	35.4	5	Antered mercentum communications, Deregulated nutrient signaling, Extracellular matrix stiffness, Genomic instability, Stem cell exhaustion	12	4	8	7	8	2	6	Antagonism*	Reported; Lifespan extension	Anti-Longevity: * daf-1 mutation in adults increased mean lifespan by up to 120% and maximum lifespan by up to 185% in <i>C. elegans.</i> Pro-Longevity: *	Antagonism	Yes	Group 1	GenAge	Tumor suppressor gene Tg/br2-deficient tumors enhanced the survival and reduced tumor weight	PMID: 17900898, PMID: 31609088
BUB1B	Pro	tein kinase	No	HC	46	7	37.7	2	Genomic instability, Impaired proteostasis	15	2	13	4	11	п	0	Antagonism	Reported; Lifespan extension	T23 mice (BUB1B overexpression) increased lifespan in mice; Hypomorphic BUB1B mice decreased lifespan by 50% in mice.	Agonism	Yes	Group 2	GenAge	Tumor suppressor gene	PMID: 23242215, PMID: 15208629
CASP8	I	Peptidase	Yes	HC	47	7	39.4	6	communications, Epigenetic shift, Genomic instability, Impaired proteostasis, Inflammation, Cellular senescence,	13	5	8	7	11	11	0	Antagonism	Reported; Lifespan extension	Anti-Longevity: * RNA interference (ced-3) in adulthood resulted in a 19% increase in mean lifespan in C. elegans .	Antagonism	Yes	Group 1	GenAge	Tumor suppressor gene Caspase-8 may either potentiate or suppress tumor malignancy. Upon activation, its main function is to promote apoptosis.	PMID: 17411345, PMID: 20817393
AURKE	Pro	tein kinase	Yes	HC	48	7	43.6	5	Genomic instability, Inflammation, Stem cell exhaustion, Telomere attrition Cellular senescence,	11	I	10	0	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. AURKA is involved in cell cycle checkpoing during healthy aging	PMID: 20624915,
MAP2K	l Pro	tein kinase	Yes	HC	49	7	43.6	3	Altered intercellular	20	0	20	10	9	6	3	Antagonism	Reported; Lifespan extension	Anti-Longevity: Trametinib inhibiting MAP2K1 increased lifespan by 12% in <i>Drosophtla</i> . Anti-Longevity: *	Antagonisum	Yes	Group 1	ge,GenAge, Geroprote	Antagonist for cancer. Constitutive expression of MEK1 (MAP2K1) caused cells to senescence.	PMID: 2023915, PMID: 10558995, PMID: 26119340, PMID: 14701721
CREBBI	P Acy	ltransferase	Yes	HC	50	7	44.1	6	communications, Cellular senescence, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis	13	0	13	7	4	2	2	Antagonism*	Reported; Lifespan extension	RNA interference increased mean lifespan up to 18% in <i>C. elegans</i> (dependent upon functional daf- 16); Knockout matants lived up to 33% longer in <i>C.</i> elegans (dependent upon functional daf-16). cep-1 deletion (gk138) (lg12501) increased lifespan in <i>C. elegans</i> .	Antagonism	Yes	Group 1	GenAge,SynergyAge	Tamor suppressor gene Both TSG and oncogenetic roles have been reported CREBBP inhibitor was investigated in colorectal adenocarcinoma (p2 withdrawn, NCT02413853)	PMID: 17895432, PMID: 19416129
TOP2A	ŀ	somerase	Yes	HC	51	7	45.6	5	Cellular senescence, Epigenetic shift, Genomic instability, Impaired proteostasis, Stem cell exhaustion America intercentuar	17	1	16	0	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. TOP2A is involved in cell cycle regulation during healthy aging. Topoisomerases regulate the topological states of DNA and important for neuron proliferation	PMID: 7980433
MAPK1	CM	IGC kinase	Yes	нс	52	7	46.3	7	communications, Cellular senescence, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction, Stem cell exhaustion, Telomere	27	0	27	9	7	4	3	Antagonism R	eported; Reduced lifespan onl	Pro-Longevity: Mpk-1 RNAi decreased lifespan in C. elegans	NA	Yes	Group 3	GenAge	Antiagonist for cancer. Age-associated selective impairment in the MAPK signaling pathways in the aged banin. Lifebang calarix restriction completely prevented the age-related decrease in basal berin FEK activity and diminished the age-related reduction of p39 MAPK activity.	PMID: 20624915, PMID: 10647963, PMID: 10538995
EP300	Acy	ltransferase	Yes	HC	53	7	50.4	8	A hered intercellular communications, Cellular senescence, Epigenetic shift, Extracellular matrix stiffness, Genomie instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction	23	0	23	6	6	4	2	Antagonism	Reported; Lifespan extension	Ami-Longevity: * RNA interference (cor-1) increased mean lifespan up to 15% in <i>Calegons</i> (dependent upon functional dat-16). Knochout matantis livedu pto 33% longer in <i>C</i> . elogons (dependent upon functional daf-16) RNA ir steukide in a mean and maximal lifespan increased by 20% and 10% respectively in <i>C</i> . elogans.	Antagonism	Yes	Group 1	GenAge	Tumor suppressor gene	PMID: 17895432, PMID: 17895432, PMID: 20346071
ERBB3	Rec	eptor kinase	Yes	HC	54	7	51.3	4	Cellular senescence, Deregulated nutrient signaling, Genomie instablity, Impaired proteostasis	11	3	8	5	11	9	2	Antagonism	Reported; Lifespan extension	Pro-Longovije: Let-23 mutnite (reduction-of-finaterion) sarvive less robusty in middle adulhood than matched widd pec control (19) decremes of mediani filespan, 8% decrease of maximum lifespan (PMID: 20497132) Let-23 mutants (gain-of-function) survive more robusty in middle adulhood (29% increase of mediani lifespan, 9% increase of maximum lifespan (PMID: 20497132)	Agonism	Yes	Group 2	GenAge	Antiggoint for cases. EPRD1 is necessary for matazation and myclination of eligodendrocytes, specialized glui eclis that myclinate CNS atoms	PMID: 35370556, PMID: 20497132
NRAS	F	lydrolase	No	HC	55	7	54.4	0	- Cellular senescence.	25	0	25	9	9	9	0	Antagonism R	eported; Reduced lifespan onl	Anti-Longevity: let-60 gain-of-function significantly reduced lifespan in C. elegans.	NA	No	-	GenAge	Target did not associate with any aging hallmarks Antagonist for cancer.	PMID: 16164423
KDM1A	Oxi	doreductase	Yes	HC	56	7	54.9	6	Deregulated nutrient signaling, Epigenetic shift, Genomic instability, Impaired proteostasis, Stem cell exhaustion Altered intercellular	27	1	26	0	10	10	0	Antagonism	Not reported	No evidence Pro-Longevity:	NA	Yes	Group 4	·	Antagonist for cancer: KDMIA, is a drug targer of IMG-729b, Nsins-specific demethylase 1 inhibitor, investigated for the treatment of leakemia in trial (NCT0342227). Modulation of KDMIA with validemstat (KDMIA inhibitor) rescues memory deficit and behavioral alterations in mice	PMID: 32469975
PRKDC	Pro	tein kinase	Yes	HC	57	7	55.1	9	communications, Cellular senescence, Deregulated nutrient signaling, Epigenetic shift, Genomic instability, Impaired proteostasis, Inflammation, Stem cell exhaustion, Telomere	29	0	29	0	11	н	0	Antagonism	Reported; Lifespan extension	Pro-Longevity: mei-41 overexpression increased lifespan in Drosophila. mei-41 mutatiedexcessed lifespan in Drosophila. Dimnished lifespan and acute stress-induced death in DNA-PKcs-deficient mice with limiting telomeres. However, a study demonstrated the anti-longevity of PRKDE of c. degoars, and alt-l decition	Agonism	Yes	Group 2	-	Antagonist for cancer. PRKDC is invovked in DNA double-strand break repair and innate immune system during healthy aging	PMID: 6411485, PMID: 14528032, PMID: 23434802, PMID: 17072335
FGFR2	Rec	eptor kinase	Yes	нс	58	7	58.7	4	A leved intercellular communications, Extracellular matrix stiffness, Genomic instability, Stem cell exhaustion	16	4	12	6	9	2	7	Antagonism*	Not reported	No evidence	NA	Yes	Group 4	-	Antagonist for cancer but our data showed FGFR2 downregulation in cancer. FGFR2 is important for cell division, cell mataration, formation of new blood vescels, wound healing, and bone growth and development	
EZH2	Meth	yltransferase	Yes	нс	59	7	59.3	4	Cellular senescence, Epigenetic shift, Inflammation, Stem cell exhaustion	9	3	6	9	11	11	0	Antagonism	Reported; Lifespan extension	Anti-Longevity: Heterogeneous mutation at antimic sociel (3)731 increased lifespan by 71% - 70%; while heterogeneous mutation at antimic sociel (3 increased lifespan by 33% in <i>Drosophila</i> . E2012 mutatins verse long-lived dee to increased resistance to oxidative stress and starvation in <i>Drosophila</i> . RNAi mes-2 increased lifespan by 6.5% in <i>C</i> elogant .	Antagonism	Yes	Group 1	GenAge,SynergyAge	EZIC is considered at oncogens in cancer. Inhibities of EZI2 attenuates neuroinflummation Mcroglial EZI2 inhibition ledds to neuroprotection after stroke in <u>https:</u> aged mice	PMID: 20018689, PMID: 2293418, PMID: 22212285, //www.ahajournah.org/doi/10.1161/str.52 suppl.1.P759
PPARA	Nuc	lear receptor	Yes	нс	60	7	61.6	11	commutaciations, Deregulated nutriculations, Deregulated nutriculations, Extracellular matrix stiffless, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Retrotranspositions, Stem	22	1	21	2	8	1	7	Agonism	Reported; Lifespan extension	Pro-Longrvity: Cloffente and Fenofibrate agonising PPARA extended lifespan in <i>C. elegans</i> .	Agonism	Yes	Group 1	JrugAge,Geroprotector	Agnisis for anover PPARy agoins, doly up-swootide motholic disease and extend longeryn, Rearflorta opening PPAR ag PAR Gestended lifespan Dearflorta opening PPAR agoing a set of the Rearflorta opening and provide the set of the Rearflorta opening and the set of the set of the Rearflorta opening and the set of the set of the Rearflorta of the set of the set of the set of the Rearflorta of the set of the set of the set of the Rearflorta of the set of the set of the set of the Rearflorta of the set of the set of the set of the set of the Rearflorta of the set of the set of the set of the set of the Rearflorta of the set of the Rearflort of the set of the Rearflort of the set o	PMID: 32219735 PMID: 25005800

HR	AS E	lydrolase	No	нс	61	7	62.9	4	Cellular senescence, Extracellular matrix stiffness, Genomic	17	10	7	10	8	7	1	Antagonism Rep	orted; Reduced lifespan only	Pro-Longevity: let-60(n1046gf) mutation decreased lifespan in C.	NA	Yes	Group 3	GenAge	Antagonist for cancer. Deregulation of the EgfriRas signaling pathway induces age-related brain degeneration in the Drosophila. Expression of IRAS in lung Forbolasts resulted in a permanent G1	PMID: 12529440, PMID: 9054499,
									instability, Inflammation Attered intercentiar communications, Cellular										elegans .					arrest, accompanied by accumulation of senescence associated factors, p53 and p16.	PMID: 16164423
AB	Li Tyn	osine kinase	Yes	HC	62	7	70.7	9	senescence, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial	16	7	9	7	9	5	4	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer but ABL 1 is important for DNA double-strand break repair during healthy aging. Senolyfic treatment roduces cell sensections: Quercetin, senolytic drug, inhibits multiple kinases including ABL 1. Pro-Longevity: Imatinib mesylate inhibiting ABL 1 reduced lifespan in <i>C. olegans</i> .	PMID: 3201088
SIR	TI Asy	ltransferase	Yes	нс	63	7	73.3	12	Abenet anenes hair sensense, Oraghade Figurates dal, and an anon and an anon sense and an anon market and an a	15	2	13	3	8	ı	7	Antagonism* Re	sported; Lifespan extension	ProLongenty: 91:21 oversensis necread first an significantly a C. degar. The second second second second second matchical by second second second second matchical by second destination of the second second second 26.1 % in <i>Drosophila</i> . Class of 4526 destination filters of the 540 matchical by second second second second 26.1 % in <i>Drosophila</i> . Class of 4526 destinations of the 576 matchical by second second second second 26.1 % in <i>Drosophila</i> . Matchical begins in mice, and concernents of default and second second destination of the second second second matchical by the second second second matchical by the second second second matchical by the second second second destination of the second second second matchical by the second second second destination of the second second second second destination of the second second second destination of the second second second destination of the second second second destination destination of the second destination destination of the second destination destination of the second destination destination of the second second destination	Agonism	Ya	Group 2	GenAge: SynergyAge	Antagonin for concer, although our data showed that fore were desamplification in 6 cancers. SRT can set as an oncogene or time represent on cancer labilities of SRT lacking symbolic data optimis. SRT can set as an oncogene or time represent on cancer labilities of SRT lacking symbolic data optimis. SRT can set as a strategiest of the set of SRT lacking symbol disease-related confirms.	PMID: 112-0165, PMID: 1230150, PMID: 20075665, PMID: 2010/96, PMID: 15977360, PMID: 15977360, PMID: 21030067, PMID: 21030067, PMID: 15930067, PMID: 15520384, PMID: 15520384, PMID: 15120384, PMID: 15120384,
PTP	RC Recept	or phosphatas	Yes	HC	64	7	81.4	4	communications, Genomic instability, Inflammation, Stem cell	15	10	5	3	8	5	3	Antagonism* Rep	oorted; reduced lifespan only	pipre decreased mespan in mice.	NA	Yes	Group 3		Tumor suppressor gene BC8 1311, antibody drug & PTPRC binding agent, was investigated in clincial trials for cancer treatment.	PMID: 30820040
TY	4S Meth	iyitransferase	Yes	HC	65	6	33.2	3	Inflammation, Mitochondrial dysfunction, Stem cell exhaustion Altered intercellular	14	8	6	0	11	11	0	Antagonism Re	eported; Lifespan extension	Anti-Longevity: Floxuridine (400 µM) extended lifespan in C. elegans, while a higher dose i.e. 5000 µM shortened their lifespans.	Antagonism	Yes	Group 1	DrugAge	Antagonist for cancer. TYMS is involved in cell cycle regulation during healthy aging.	PMID: 153363
RA	C1 E	Iydrolase	No	HC	66	6	38.5	6	Altered intercellular communications, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Inflammation Amered intercensuar communications, Cellular	16	1	15	9	10	9	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4	·	Antagonist for cancer. RAC1 is involved in adaptive immune system and innate immune system during healthy aging.	
SR	C Tyn	osine kinase	Yes	нс	67	6	47.5	11	senescence, Deregulated nutrien signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Stem cell	10	3	7	6	8	7	1	Antagonism	Not reported	Not reported	NA	Yes	Group 4		Antagonist for cancer. Dasatisib, SRC inhibitor, was used for cancer treatment. Dasatish was also considered a searchytic used to remove senercent cell.	
CDC	25A	Esterase	No	HC	68	6	49.3	2	Genomic instability, Impaired proteostasis Anerea intercentuar communications, Deregulated nutrient	16	1	15	1	11	11	0	Antagonism Re	eported; Lifespan extension	Anti-Longevity: cdc-25.3 (RNAi) significantly increased lifespan in <i>C. elegans</i> .	Antagonism	Yes	Group 1	GenAge	Antagonist for cancer. CDC25A is thought to be a proto-oncogene. CDC25A is invovled for cell cycle regulation.	PMID: 16741121, PMID: 15021892
IL.	B b	nterleukin	Yes	HC	θ	6	49.5	8	signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Telomere	9	1	8	6	6	3	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		IL-1α and IL-1β signal upregulate the senescence-associated secretory phenotype in a cooperative manner. IL-1β promotes the age-associated decline of beta cell function.	PMID: 36988157, PMID: 34746709
FGF	R1 Rec	eptor kinase	Yes	HC	70	6	49.8	5	Cellular somescence, Deregulated nutrient signaling, Extracellular matrix stiffness, Genomic instability, Telomere attrition suscess nucescensus communications, Cellular	16	11	5	7	8	1	7	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		FGFR1 antagonists such as pemigatinb approved for cancer (NCT0011372) but our data showed FGFR1 upregulation is cancers. Nice with an attenuation of FGFR1 in mix-ganing develop deletes with age and exhibit a decreased number of beta-cells, and lower levels of FGFR1 in mix-have also hear ne leaded to cranificial defects.	PMID: 12514106, PMID: 11130726
K	T Rec	eptor kinase	Yes	HC	71	6	51.8	6	senescence, Deregulated nutrient signaling, Genomic instability, Inflammation, Stem cell	17	5	12	6	10	2	8	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		cancer. Adult myocardium refect on c.kit expression to regenerate after injury and to counteract aging effects on cardiac structure and function. Imatinib mesylate inhibiting PDGFRB, ABL1, KIT, BCR reduced lifespan is C. olegans.	PMID: 31275242, PMID: 32010883
RA	tB Nuc	lear receptor	Yes	HC	72	6	54.8	2	Genomic instability, Stem cell exhaustion	14	6	8	0	10	1	9	Agonism	Not reported	No evidence	NA	Yes	Group 4		Agonist for cancer. RAR agonist ameliorated the UV-induced damage to skin collagen fibers, and increased the collagen content in photoaged skin through RAR.	PMID: 28849147
MAI	K8 CN	4GC kinase	Yes	HC	73	6	57.0	6	Cellular senescence, Epigenetic shift, Genomic instability, Impaired protoestasis, Mitochondrial dysfunction, Stem cell exhaustion	16	1	15	0	7	3	4	Antagonism Re		Pro-Longevity: loss-of-funtion jnk-1 significantly decreased lifespan in C. chegara. jnk-1 overpression (lph2) increased lifespan in C. elegara: jnk-1 deficient mice (gk1) decreased lifespan. Bek RNAi decreased lifespan bj Ch 4% in male and 10.2% in female Drosophtla.	Agonism	Yes	Group 2	GenAge, SynergyAge	Antagonia for cancer. Targerian (JNK JNK Ninterferences and inhibitor inhibit the development of Populoschilar carcinoma. MAPK, also karow an JNK 1 Frurt filter with matations that argument JNK signaling for longer. MAPKs inhibitor was moreigated in an mychold takemia (of terminated, NC10012889)) Antagonia for cancer.	PMID: 28012230, PMID: 15767565, PMID: 18832074, PMID: 20976250
СТ	iB I	Peptidase	No	HC	74	6	58.8	3	Extracellular matrix stiffness, Genomic instability, Impaired proteostasis	17	0	17	1	11	8	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Inhibitors of cathepsin B improve memory and reduce beta-amyloid in transgenic Atheimer disease mice. Nucleus distribution of cathepsis B is sensector microfila promotes brain aging through degradation of sirtuins.	PMID: 18184638, PMID: 33049518
DN	42 F	lydrolase	No	HC	75	6	61.2	5	Altered intercellular communications, Cellular senescence, Deregulated nutrient signaling, Extracellular matrix stiffness, Genomic instability	13	3	10	3	10	6	4	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-	Tumor suppressor gene	
RĐ	DA E	Iydrolase	No	нс	76	6	63.5	5	Altered intercellular communications, Epigenetic shift, Genomic instability, Inflammation, Stem cell exhaustion	11	1	10	9	6	3	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. RHOA is involved in protecting against the progression of cardiac aging.	https://escholarship.org/uc/item/14g0843j

JAK2 Ty	rosine kinase	Yes	нс	77	6	67.2	9	Ahered intercellular communications, Cellular senescence, Deregulated nutrient signaling, Epigeneici shift, Extracellular matrix stiffness, Genomic instability, Inflummation, Retrotranspositions, Stem	14	3	11	6	8	1	7	Antagonism*	Reported; Lifespan extension	Anti Longevity: Heterogeneus gais-of-function decreased lifespan significantly in Dorosphila Heterogeneos ito-of-function bereared lifespan significantly increased in Drosophila.	Antagonism	Yes	Group 1	GenAge	Resultinh, JAC2 antegonie wa investigated for cancer treatment. Inhibition of the JAK pathway particip restored agr-related decline in coordination.	PMID: 22291607, PMID: 26578790
AKT3 A	AGC kinase	Yes	нс	78	6	71.3	3	cell exhaustion Cellular senescence, Mitochondrial dysfunction, Retrotranspositions Altered intercellular	25	6	19	9	10	3	7	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		AKT3 antagonist such as Capivaserth investigated for cancer but our data showed AKT3 downregulation in cancer. Aging-induced Alt activation involves in aging-related pathologies and Aβ-induced toxicity	PMID: 31183966
PKM Non	a-protein kinase	No	HC	79	6	73.2	5	communications, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Mitochondrial dysfunction	16	1	15	0	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. PKM is involved in innute immune system during healthy aging. In addition, loss of PFMM impairs angiogenis reprosting and loss of endothelial PKM2 alters mitochondrial metabolism.	PMID: 30301887
PGR Na	aclear receptor	Yes	нс	80	5	22.8	2	Altered intercellular communications, Mitochondrial dysfunction	17	12	5	0	9	0	9	Agonism	Reported; Lifespan extension	Pro Longevity: Danazol agonising PGR & AR extended lifespan in <i>C. elegans.</i>	Agonism	Yes	Group 1	JrugAge,Geroprotector	PGR against sere investigated for cancer treatment such as breast cancer, endownizit cancer, poster cancer, low cancer, Progetores has multiple non-sprokentic functions in the central mich-choreal function, neurogenetics and regreseration, mich-discubil function, neurogenetics and regreseration, mich-discubil function, neurogenetics and regreseration, attemption for encourse from transmits brain nieury. Attemption for encourse from transmits brain nieury. Attemption for encourse from transmits that nieury. Attemption for encourse from the state of profileration. NCOA promote house tasset: of profileration LCF1.	PMID: 18374402, PMID: 24134630
NCOA3 Ac	cyltransferase	No	нс	81	5	37.2	2	Epigenetic shift, Stem cell exhaustion	17	2	15	1	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Inhibition of XPC0A3 could prevent the dovelapment of fibrosis, and anchorate pre-scatabilded fibrosis. NOCA3 overapression in the non-stumonal HEX33 cells habits the premature sense-create induced by hydogen previde or mapraysin. The mechanism involves (1) the inhibition of antiphagy and (2) the increase in level and locateral acadiators (50 obth for edl cy cell suppression p2): Provide and and SIRTI. PCOAD overapressions in engligid noder for minitis the telemense activity. NCOA3 are interpression of sensecure whose downregulation in aged	PMID: 23511556, PMID: 26469953
NCOA1 Ac	cyltransferase	No	нс	82	5	43.6	5	Altered intercellular communications, Deregulated nutrient signaling. Fogienetics shift, Genomic instability, Mitochondrial dysfunction centual reservence,	23	6	17	1	8	1	7	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		individuali could reprobably rumor suppressor machinism, preventing the docal creations of risk yold cells from huving damaged DNA. Antagonist for cause I could be compared to the star numer. Aging or FR antidage serves shown is do do numerican 17)berntalial treatment cause prepulse NCOAI. Best-Entraled was above to increase lifetopan is of cologram. Taken together, NCCAI agonist may delay aging. NCOAI is recursed for the anti-obsequence lifetopan is of the anti-obsequence.	PMID: 26287601, PMID: 24134630
ATM Pr	rotein kinase	No	нс	83	5	44,4	10	Deregulated nutrient signaling, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Retrotranspositions, Stem	13	11	2	7	7	4	3	Antagonism	Reported; Lifespan extension	Pro-Longovity: Lidegran of Tex-X- Ann-s significantly decreased comparing to Tex-X-ann-i-Hate generation mice. Mutations is a AVM in late-generation TEXC mutants with short telometers resulted in signs of permainter ageing Anni-Longovity: Deletion alleke ann (Lejk189) increased lifespan by 20% in <i>C. elegans</i> .	nism / Antagon	Yes	Group 2	SynergyAge,GenAge	Turner suppressor para Low dote of chalenqueir (sub-hite) and hite gene (proteins)) scivites (TAT, promoted DNA damage learners, rescued age-related metabolic shift, and prolonged replicative lifespan in mice.	PMID: 12540856, PMID: 19416129
EphA2 Ro	cceptor kinase	Yes	HC	84	5	47.6	5	Cellular senescence, Extracellular matrix stiffness, Genomic instability, Inflammation, Telomere attrition A neteca intercentuar communications,	8	5	3	4	10	4	6	Antagonism	Reported; Lifespan extension	Pro-Longevity: vab-1 overexpression (dx31) increased lifespan by 20% in <i>C. elegans</i> .	Agonism	Yes	Group 2	GenAge	Antagonist for cancer, EphA2 as a promoter of melanoma tumorigenicity	PMID: 19853560, PMID: 19223760
HDAC2	Hydrolase	Yes	нс	85	5	48.6	7	Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis,	23	1	22	1	9	9	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antigonist for cancer. HDAC2 inhibitors, venionstat and romidepain were approved for the treatment of cuanous. T-cell symphoma, Inactivating histone deatectylate HDA promotes longevity by mobilizing trehalose metabolism.	PMID: 33790287
RARA Nu	sclear receptor	Yes	HC	86	5	50.6	6	Altered intercellular communications, Cellular senescence, Epigenetic shift, Genomic instability, Inflammation, Stem cell exhaustion Aneree intercenturar	13	10	3	0	8	4	4	Agonism	Not reported	No evidence	NA	Yes	Group 4	-	RARA agonist for cancer. RAR agonist anelonated the UV-induced damage to skin collagen fibers, and increased the collagor content in photoaged skin through RAR.	PMID: 28849147
AKT2 A	AGC kinase	Yes	нс	87	5	57.8	7	communications, Deregulated nutrient signaling, Epigenetic shift, Gencomic instability, Mitochondrial dysfunction, Retrotranspositions.	17	5	12	9	7	4	3	Antagonism	Reported; Lifespan extension	Anti-Longevity: AKT2 knockout mutants increased lifespan by 9.1% in mice.	Antagonism	Yes	Group 1	GenAge	Aging-induced Alt activation involves in aging-related pathologies and A\beta-induced toxicity	PMID: 28681509, PMID: 31183966
DNMT3A Met	thyltransferase	Yes	нс	88	5	60.0	3	Deregulated nutrient signaling, Epigenetic shift, Genomic instability Azeree intercentuar communications, Cellular senescence, Deregulated	16	3	13	7	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-	Constitutive loss of DNMT3A causes morbid obesity through misregulation of adipogenesis	PMID: 35635747
TNF umou	ur necrosis facă	Yes	нс	89	5	61.6	11	nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Stern cell	9	I	8	8	7	4	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		TNF angoints were investigated for cancer treatment but our data showed TNF downspecification in cancer. TNF our near the treatment of the treatment of the treatment y yearry amplify exerciscore-associated feathermation. TNF-deficient mice develop normally but are more susceptible to some infectious agains.	PMID: 34076259, PMID: 35645319
PLAU	Peptidase	No	нс	90	5	62.2	2	Extracellular matrix stiffness, Impaired proteostasis	8	4	4	6	10	9	1	Antagonism	Reported; Lifespan extension	Pro-Longevity: uPA overexpression (alphaMUPA) increased lifespan by 20% in mice. Transgenic mice overexpressing urokinase-type plasminogen activator increased longevity.	Agonism	Yes	Group 2	GenAge	Antagonist for cancer.	PMID: 9060969, PMID: 10638529
ΠGAV	Receptor	Yes	нс	91	5	66.2	7	Akered intercellular communications, Cellular senescence, Dereguladed nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Genomie instability, Retrotranspositions	21	7	14	5	10	7	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Siloncing of ITOM Shall and professions, invasion, and self- researia of breast career cell lines. ITOR's served as a signal for L/Y sil, a nodecul stimulating the pedaction of ILA, which is considered an angle profession of the siloncia	PMID: 32064162, PMID: 17071038, PMID: 22547695

								Centuar senescence,																
								Epigenetic shift, Genomic instability, Impaired										Pro-Longevity:					Antagonist for cancer.	
APEX1	Esterase	Yes	HC	92	5	67.8	8	proteostasis, Inflammation, Mitochondrial dysfunction, Stem cell	27	0	27	1	10	9	1	Antagonism F	eported; Reduced lifespan only	exo-3 (RNAi) decreased lifespan by 20% in C. elegans.	NA	Yes	Group 3	GenAge	Antagonast for cancer. APEX1 is invovled in base excision repair during healthy aging	PMID: 20346071
UBE2C	Acyltransferase	No	HC	93	5	70.8	1	Impaired proteostasis Anerea intercentuar	9	2	7	0	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. UBE2C is involved in cell cycle checkboints during healthy aging	
GSTP1	Transferase	Yes	нс	94	5	71.0	7	communications, Epigenetic shift, Extracellular matrix stiffness, Genomic	22	9	13	1	10	6	4	Antagonism	Reported; Lifespan extension	Pro-Longevity: Overexpression of gst-10 increased lifespan by around 22% in C. elegans.	Agonism	Yes	Group 2	GenAge,Paper	GSTP1 antagonist such as ezatiostat was investigated for cancer treatment.	PMID: 30043549, PMID: 16164425, PMID: 17157356
								instability, Inflammation, Mitochondrial										GSTP1 RNAi extended lifespan in C. elegans .					GSTP1 overexpression protects against UV light damage.	PMID: 17157356
HMGB1	Chemokine	Yes	HC	95	5	71.0	7	communications, Cellular senescence, Extracellular matrix stiffness, Genomic instability, Impaired	15	4	11	1	6	4	2	Antagonism	Not reported	No evidence	NA	Yes	Group 4		diffuse large B-cell lymphoma. HMGB1 mediates neuroinflammatory priming in the aged brain. Blocking the actions of HMGB1 appears to "desensitize" aged microglia to an immune challenge,	PMID: 30988279, PMID: 27466339
								proteostasis, Inflammation, Attered intercentuar communications, Cellular senescence, Deregulated nutrient signaling,															thereby preventing exaggerated behavioral and neuroinflammatory responses following infection	
PTK2	Tyrosine kinase	Yes	HC	96	5	76.8	9	Extracellular matrix stiffness, Genomie instability, Impaired proteostasis, Inflammation, Retrotranspositions,	19	5	14	6	9	9	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. PTK2 is involved in innute immune system during healthy aging.	
DNMT3B	Methyltransferase	No	нс	97	4	37.5	1	Epigenetic shift	6	2	4	1	11	10	1	Antagonism	Not reported	No evidence	NA	No	Group 4	-	Antagonist for cancer as DNMT3B silencing suppresses migration and invasion by epigenetically promoting mile.34a in bladder cancer. DNMT3B plays a protective role against hepatocarcitogenesis caused by chronic inflummation via maintaining mitochondrial homeostasis.	PMID: 33221743, PMID: 33277576
FAS	Receptor	No	HC	98	4	39.3	3	communications, Genomic instability,	24	23	1	8	10	2	8		eported; Reduced lifespan only	mice	NA	Yes	Group 3		by enronic infummation via maintaining mitoenondriai nomeostasis. Tumor suppressor gene	PMID: 26084385
RRM2	Oxidoreductase	Yes	HC	99	4	43.8	1	Genomic instability	14	2	12	2	11	11	0	Antagonism	Reported; Lifespan extension	Anti-Longevity: rnr-2 (RNAi) increased lifespan by 14.2% in C. elegans.	Antagonism	Yes	Group 1	GenAge	Antagonist for cancer. RRM2 is involved in DNA replication during healthy aging	PMID: 23144747
PTGS2	Oxidoreductase	Yes	нс	100	4	44.3	4	Altered intercellular communications, Extracellular matrix stiffness, Genomic	9	8	1	7	9	4	5	Antagonism*	Reported; Lifespan extension	Anti-Longevity: Aspirin inhibiting PTGS1 and PTGS2 extended lifespan in mice.	Antagonism	Yes	Group 1)rugAge,Geroprotector	Increased senescence in PTGS2/COX2 transgenic mice. Cyclooxygenase-2 inhibitors modulate skin aging in a catalytic activity- independent manner.	PMID: 27750221, PMID: 22771771, PMID: 18631321
								instability, Inflammation A newco untercenuar communications, Celhalar senescence, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix																
LYN	Tyrosine kinase	Yes	Novel	1	11	4.5	11	stiffness, Genomic instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction, Akered intercellular	9	2	7	2	7	6	1	Antagonism	Not reported	Not reported	NA	Yes	Group 4		Lyn suppresses osteoclastogenesis in vitro and in vito.	PMID: 19171907
PTPN11	Esterase	Yes	Novel	2	11	13.5	7	communications, Cellular senescence, Deregulated nutrient signaling, Epigenetic shift, Extracellular matrix stiffness, Impaired proteostasis, Inflummation	21	1	20	8	10	7	3	Antagonism l	Reported; reduced lifespan only	Pro-Longevity: ptp-2 RNAi decreased lifespan in C elegans.	NA	Yes	Group 3		Antagonist for cancer. PTPN11 is involved in adaptive immune system during healthy aging. In addition, the PTPN11 loss-of-function mutation Q510E-Shp2 causes hypertrophic cardioparthy by dysregulating m TOR signaling	PMID: 22058153, PMID: 16547100
POLE	Transferase	Yes	Novel	3	11	13.9	2	Cellular senescence, Genomic instability	18	3	15	1	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-	Tumor suppressor gene	
PKMYT1	Protein kinase	No	Novel	4	11	14.5	0		16	1	15	0	10	10	0	Antagonism	Not reported	No evidence	NA	No			Target did not associate with any aging hallmarks	
HCK	Tyrosine kinase	Yes	Novel	5	11	14.9	4	Extracellular matrix stiffness, Genomic instability, Impaired	17	5	12	2	11	6	5	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer.	
POLA1	Transferase	Yes	Novel	6	11	18.8	2	proteostasis, Inflammation Cellular senescence, Genomic instability	23	4	19	0	8	8	0	Antagonism F	eported; Reduced lifespan only	Pro-Longevity: Y47D3A.29 RNAi decreased lifespan by 25.68% in <i>C. elevans</i> .	NA	Yes	Group 3	GenAge	Antagonist for cancer. POLA1 is involved in cell cycle regulation and DNA replication initiation. Antagonist for cancer but HDAC10 was demonstrated to be a tumor	PMID: 18059442
HDAC10	Hydrolase	Yes	Novel	7	11	19.7	5	Cellular senescence, Epigenetic shift, Genomic instability, Impaired proteostasis, Mitochondrial dysfunction	15	14	1	0	5	4	I	Antagonism	Not reported	No evidence	NA	Yes	Group 4		suppresser in some types of cancer. Highly tunnorignen and etem-like lung addressaricionan coeff were increased in Hdae:10 deleted tunnor compared with Hdac10 wild-type tunnors. HDAC10 expression is associated with DNA minmatch repair gene and is a predictor of godd prognostin is cocho arcticoma Reduced expression of HDAC10 contributes to tunnor progression in SSCLC.	PMID: 32540961, PMID: 29083502
IMPDH2	Oxidoreductase	Yes	Novel	8	11	23.2	0		5	1	4	0	10	5	5	Antagonism I	teported; No effects on lifespar	Anti-Longevity: Mycophenolic acid inhibiting IMPDH1 and IMPH21 increased lifespan by 6.68% in <i>Drosophila</i> without significance. Mycophenolic acid inhibiting IMPDH1 and IMPH2 slightly increased lifespan by 6.68% in C. elegans without significance. Pro-Longevity:	NA	No			Target did not associate with any aging hallmarks < 7 tissues (out of 47) dystegalated during aging	PMID: 33008901
PSMD14	Peptidase	Yes	Novel	9	11	23.9	3	Cellular senescence, Genomic instability, Impaired proteostasis	21	1	20	1	11	10	1	Antagonism F	eported; Reduced lifespan only	nost-developmental RNAi of mt-1 decreased	NA	Yes	Group 3	GenAge, SynergyAge	Antagonist for cancer. PSMD14 is invovled in cell cycle checkpoint.	PMID: 23144747, PMID:17392428
																							Overexpression of FES could inhibit cell proliferation, migration, and invasion of osteosarcoma cells. However, FES is considered as proto-oncogene, tyrosine kinase, and	PMID: 322556211,
FES	Tyrosine kinase	No	Novel	10	11	28.4	1	Inflammation	16	13	3	7	10	3	7	Antagonism*	Not reported	No evidence Pro-Longevity: pbs-5 overexpression increase 25% lifespan in <i>C</i> .	NA	Yes	Group 4	-	our data showed FES downregalation in 3 cancers. Taken together, its expression dysregulation is inconsistent with its mechanism of action in cancer. FES kinase activity is also dispensable for hematopoiesis.	PMID: 10523632
PSMB5	Peptidase	Yes	Novel	11	11	32.4	2	Genomic instability, Impaired proteostasis	27	0	27	1	8	8	0	Antagonism	Reported; Lifespan extension	piss-3 overexpression increase 23% intespin in C. elogans. phs-5 RNAi decreased lifespan by 29.95% in C. elogans.	Agonism	Yes	Group 2	GenAge	Antagonist for cancer. PSMB5 is involved in cell cycle checkpoint during heahly aging. Antagonist for cancer but SM0 inhibition promotes aging. SMO has shown to be critical for the hedgebog signal mandauction on	PMID: 25395451, PMID: 17392428
SMO	GPCR	Yes	Novel	12	11	43.5	3	Genomic instability, Impaired proteostasis, Stem cell exhaustion	17	12	5	2	7	3	4	Antagonism	Not reported	No evidence	NA	Yes	Group 4		the cell membrane. Hedgebog signaling is dyrergulated in old heptocyclss, and this accentrace sign: Deleting SMO in young hepatocytes before partial hepatectomy prevented hedgehog pathway activation after partial hepatectomy and inhibited regressreation. In addition, hedgehog inhibition promoted telomers shortening and mitochondral dysfunction in hepatocytes.	PMID: 34984806
MCM8	Hydrolase	No	Novel	13	10	23.8	3	Cellular senescence, Genomic instability, Impaired proteostasis	11	4	7	0	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. MCM8 is invovled in cell cycle checkpoint during healthy aging.	

																		Pro-Longevity:						
PSMB2	Peptidase	Yes	Novel	14	10	23.9	1	Impaired proteostasis	26	0	26	1	10	10	0	Antagonism R	eported; Reduced lifespan only	pbs-4 RNAi decreased lifespan by 30.92% in C. elegans.	NA	Yes	Group 3	SynergyAge	Antagonist for cancer. PSMB2 is invovled in cell cycle checkpoint during healthy aging.	PMID:17392428
PRIM1	Transferase	Yes	Novel	15	10	27.0	1	Genomic instability	21	2	19	0	9	9	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4	-		
FGR	Tyrosine kinase	Yes	Novel	16	10	31.7	5	Cellular senescence, Deregulated nutrient signaling, Extracellular matrix stiffness,	18	10	8	2	7	3	4	Antagonism*	Not reported	No evidence	NA	Yes	Group 4		FGR inhibitor, such as dasatinib was investigated for cancer, although our data showed FGR downregulation in cancers. Dasatinib and querectin restore a-Klotho in mice and humans, which	PMID: 35292270
								Inflammation, Mitochondrial dysfunction															may amplify protection against aging and age-related diseases. TOP2B inhibitor such as Etoposide approved for cancer, although our data showed TOP2B downregulation in cancer TOP2B is key detachenting enzyme that alses TDAY topology by	
TOP2B PSMA4	Isomerase	Yes	Novel	17	10	34.7 38.7	1	Epigenetic shift	24	0	24	0	5	4	1	Antagonism*	Not reported	No evidence	NA NA	Yes	Group 4 Group 4	•	binding to two double-stranded DNA molecules. Antagonist for cancer.	
GNB1	Hydrolase	No	Novel	19	10	39.3	0	impared processases	28	2	26	6	9	7	2	Antagonism	Not reported	No evidence	NA	No	-		PSMA4 is invovled in cell cycle checkboint during healthy aging. Target did not associate with any aging hallmarks	
PSMA3	Peptidase	Yes	Novel	20	10	39.7	1	Impaired proteostasis	19	0	19	1	9	9	0		teported; No effects on lifespar	Anit-Longevity: pas-7 RNAi slightly increased lifespan by 1.93% without significance in <i>C. elegans.</i>	NA	Yes	Group 4	SynergyAge	Antagonist for cancer. PSMA3 is involved in cell cycle checkpoint during healthy aging.	PMID:17392428
KDM2A	Oxidoreductase	No	Novel	21	10	45.9	3	Cellular senescence, Epigenetic shift, Genomic instability	12	1	11	0	8	7	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. KDM2A promotes stemmess and angiogenesis of breast cancer. KDM2A deficiency in macrophages enhances thermogenesis to protect mice against HFD-induced obesity.	PMID: 27029061, PMID: 33462408
UBE2T	Acyltransferase	No	Novel	22	9	21.7	2	Cellular senescence, Impaired proteostasis	20	2	18	0	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. UBE2T is invovled in DNA repair (fanconi anemia pathway) during healthy aoing	
ITGB5	Receptor	Yes	Novel	23	9	24.2	2	Altered intercellular communications, Extracellular matrix stiffness	17	7	10	5	7	6	I	Antagonism R	eported; Reduced lifespan only	Pro-Longevity: Post-developmental RNAi of pat-3 shortens lifespan of wild type <i>C. elegans.</i>	NA	Yes	Group 3	GenAge	ITGB5 is a TGF-β activator. TGF-β signaling was shown to repress body size as well as lifespan <i>in vivo</i> . ITGB5 served as a lignal for Cyr0, in amlecule stimulating the production of IL-d ₀ , which is considered an aging biomarker, via igarvilgb5/AkrNF-κB signaling pathway in theumatoid arthritis.	PMID: 29070608, PMID: 17071038, PMID: 22547695, PMID: 23144747
WWP1	Acyltransferase	No	Novel	24	9	34.7	1	Impaired proteostasis	25	6	19	0	8	7	1	Antagonism	Neported; Lifespan extension	Pro-Longevity: wwp-1 overexpression increased lifespan by 20% in <i>C. elegans</i> wwp-1 RNAi decreased lifespan by 9% in <i>C.</i> elegans.	Agonism	Yes	Group 2	GenAge.SynergyAge	Antagonist for cancer. PTEN tunos uppresso for cancer treatment can be reactivated through inhibition of a MYC-WWP1 inhibitory pathway, unleashing tumor appressive activity WWP1 negatively regulates coacheds franction by inhibiting ostooblast differentiation and migration. WWP1 contributes to shifts in markity protofilss and a	PMID: 19553937, PMID: 18006689, PMID: 32822210,
								мастеа пистеенная										WWP1 homolog in C. elegans was found to increase life expectancy in response to dietary restriction					WWP1 contributes to shifts in matrix proteolytic profiles and a myocardial aging phenotype with diastolic heart. Inducing WWP1 expression caused LVH and preserved systolic function but impaired distols dysfunction, consistent with the phenotype of heart failure with a preserved ejection fraction.	PMID: 31097636, PMID: 23553732
ITGA9	Receptor	No	Novel	25	9	46.7	2	communications, Extracellular matrix Cellular senescence,	24	3	21	4	8	2	6	Agonism	Not reported	No evidence	NA	Yes	Group 4	-	ITGA9 suppressed hepatocellular carcinoma metastasis.	PMID: 29951557
PPP5C	Esterase	No	Novel	26	9	48.2	5	Epigenetic shift, Genomic instability, Impaired proteostasis. Inflammation	22	1	21	2	7	7	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. PPP5C is invovled in DNA double-strand break repair during healthy aging. Antaeonist for cancerr.	
ANAPC2	Acyltransferase	No	Novel	27	9	54.6	1	Impaired proteostasis	12	1	11	0	8	5	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		ANAPC2 is involved in cell cycle checkpoint during healthy aging. The anaphase promoting complex is required for memory function in mice	PMID: 21191042
MSTIR	Receptor kinase	Yes	Novel	28	9	59.2	2	Inflammation, Telomere attrition	9	4	5	0	10	6	4	Antagonism	Not reported	No evidence	NA	Yes	Group 4		MST1R kinase accelerates panereatic cancer progression via effects on both epithelial cells and macrophages. MST1R inhibitor networks bone ostatolvisi. KAT6A belongs to histone acetyltransferase (HAT). Stability of HATs and histone deacetylases activities is necessary to maintain normal cellular functions or otherwise leads to aging.	PMID: 30967626, PMID: 28248933
KAT6A	Acyltransferase	No	Novel	29	9	59.9	3	Cellular senescence, Epigenetic shift, Genomic instability	13	4	9	0	6	4	2	Antagonism	Not reported	No evidence	NA	Yes	Group 4		KATAA was found to regulate NrLARE signaling pathway and inhibit ROS accumulation in hore narrow-derived nesembyrnal stem cells from the old, then promoting profilerations, codely of formation, and cotogenic differentiation of OBMSCs. KATAA could promote ontoogenesis of OBMSCs. However, for cancer, RATAA inhibitar WM-1110 represends the cell moliferitation of orchem-avisitud IFCC offset, which orcertarression of	PMID: 19818845, PMID: 33541408, PMID: 34808502
UBE2M	Acyltransferase	No	Novel	30	9	60.1	2	Genomic instability, Impaired proteostasis Cellular senescence.	13	3	10	0	9	8	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Trolleration of contember 364 where the overexpression of KAT6A could reverse the effect in the cells. Antigonis for camer. UBE2M is involved in adaptive immune system during healthy aging.	
MAPKAPK:	Protein kinase	Yes	Novel	31	8	35.0	4	Genomic instability, Stem cell exhaustion, Telomere attrition	22	1	21	2	11	11	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonsit for cancer. MAPKAPK5 is also considered as tumor suppressor serine/threonine- protein kinase involved in mTORC1 signaling.	
ADRA2C	GPCR	Yes	Novel	32	8	43.6	1	Altered intercellular communications	11	3	8	0	9	3	6	Agonism	Not reported	No evidence	NA	Yes	Group 4		Our data showed ADRAC downregulation in multiple cancers. Decandetomismin, Clonidine, and Brinnoidine, being ADRAC agonists, were used for cancers in clinical trials. Guanfarien by whothwheid agonism, ADRACA, ANRACB, and ADRAC2 extended lifespan in C. elegans. TK inhibitor was suspended for cancer treatment that our data showed	PMID: 32632241, PMID: 30201375, PMID: 24134630
ПК	Tyrosine kinase	Yes	Novel	33	8	45.1	2	Altered intercellular communications, Inflammation Altered intercellular communications, Cellular	15	13	2	2	6	3	3	Antagonism	Not reported	No evidence	NA	Yes	Group 4		ITK inhibito was suggested for cancer treatment but our data showed ITK downregulation in cancers ITK is important for adaptive immune system during healthy aging, bit29a fiel? mult mutation decreased lifespan in <i>Drosophila</i> . Bik29A is the sole Tee family member in <i>Drosophila</i> , including itk.	PMID: 23672610, PMID: 16023106
BLK	Tyrosine kinase	Yes	Novel	34	8	48.0	6	senescence, Deregulated nutrient signaling, Epigenetic shift, Genomic instability, Inflammation	9	4	5	0	9	4	5	Antagonism*	Not reported	No evidence	NA	Yes	Group 4			
RBCK1	Acyltransferase	No	Novel	35	8	48.9	4	Epigenetic shift, Genomic instability, Impaired proteostasis, Inflammation	17	11	6	0	10	10	0	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. Knockdown RBCK1 reduced tumorigenicity in renal cancer <i>in v1vo</i> . RBCK1 depletion increases p53 protein levels and p53 target genes, and RBCK1 interacts with PTEN (tumor suppressor geen) and promotes	PMID: 30874541, PMID: 35174471
PFKP	Unclassified kinase	No	Novel	36	8	50.5	0		17	4	13	2	9	8	1	Antagonism	Not reported	No evidence	NA	No			RBCK1 interacts with PTEN (tumor suppressor geen) and promotes PTEN degradation in K48-linked ubiquitination. Tareet did not associate with any aeine hallmarks Antazonist for cancer.	
RPS6KA4	AGC kinase	No	Novel	37	8	56.9	4	Epigenetic shift, Genomic instability, Impaired proteostasis. Inflammation	18	0	18	4	10	9	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		RP56KA4 is a potentially valuable molecule for understanding HCC tumorigenesis. Increased RP56KA4 might be a promising prognostic factor for low survival of bepatocellular carcinoma. Depletion of 56k1 resembles gene expression patterns of caloric restriction or prolongs lifespato by pharmacological activation of	PMID: 35232347, PMID: 19797661
																							AMPK in mice.	
ATAD2	Hydrolase	No	Novel	38	8	63.5	0		16	2	14	0	11	11	0	Antagonism	Not reported	No evidence Pro-Longevity:	NA	No			Target did not associate with any aging hallmarks Antagonist for cancer.	
PSMB3	Peptidase	Yes	Novel	39	7	23.4	1	Impaired proteostasis	19	1	18	1	10	9	1	Antagonism R	eported; Reduced lifespan only		NA	Yes	Group 3	SynergyAge	Antagonist for cancer. PSMB3 is involved in cell cycle checkpoint during healthy aging.	PMID:17392428
PSMB6	Peptidase	Yes	Novel	40	7	33.4	1	Impaired proteostasis	21	0	21	1	8	4	4	Antagonism	Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. PSMB6 is invovled in cell cycle checkpoint during healthy aging. Our data showed PTP8F impremulation in multitude cancers, successing	
PTPRF &	eceptor phosphatas	No	Novel	41	7	33.4	1	Stem cell exhaustion	26	4	22	3	9	8	1	Antagonism	Not reported	No evidence	NA	Yes	Group 4		antagonist for cancer treatment, but PTPRF as a novel tumor suppressor through deactivation of ERK1/2 signaling in gastric adenocarcinoma, and PPARy inhibits breast cancer progression by upregulating PTPRF	PMID: 30464527, PMID: 31799666
PSMC3	Hydrolase	Yes	Novel	42	7	34.1	1	Impaired proteostasis	19	1	18	1	9	9	0	Antagonism R	eported; Reduced lifespan only	Pro-Longevity: rpt-5 RNAi decreased lifespan by 38.65% in C. elegans .	NA	Yes	Group 3	SynergyAge	expression Antagonist for cancer. PSMC3 is involved for cell cycle checkpoint during healthy aging.	PMID:17392428

PRPF19	ə Acy	yltransferase	No	Novel	43	7	35.9	3	Cellular senescence, Genomic instability, Impaired proteostasis	27	1	26	0	10	9	1	Antagonism Reported; Lifespan extensio	Pro-Longevity: n Ubiquitous overexpression of dPrp19 increased lifespan of female in <i>Drosophila</i> while inconsistent lifespan extention in male.	Agonism	Yes	Group 2	GenAge	Antagonist for cancer. PRPF19 is invovled for nucleotide excision repair during healthy aging. Agonist for cancer.	PMID: 28649423
RPS6KA2	12 AI	AGC kinase	Yes	Novel	44	7	37.7	3	Altered intercellular communications, Genomic instability, Impaired proteostasis	20	1	19	2	10	2	8	Antagonism* Not reported	No evidence	NA	Yes	Group 4		Re-expression of RPS6KA2 in ovarian cancer cell lines suppressed colony formation. In UCI101 cells, RPS6KA2 decreased proliferation, caused G1 arrest, and enhanced apoptosis. However, enverties a well as charmancological inhibition of RPS6KA2	PMID: 27028868, PMID: 16878154, PMID: 24403857
PSMC4	ын	Hydrolase	Yes	Novel	45	7	43.4	1	Impaired proteostasis	18	0	18	1	10	10	0	Antagonism Not reported	No evidence	NA	Yes	Group 4		by the inhibitor BI-D1870 acted synergistically with erlotinib on tumor cell survival Antagonist for cancer. PSMC4 is involved in cell cycle checkpoint during healthy aging.	
PSMC2		Underland	V	Neural		1	44.7			21		20					Antonio Deserve Deduced Mesons	Pro-Longevity: nly rpt-1 RNAi decreased lifespan by 36.23% in	NA	V	Group 3	GenAge,SynergyAge	Antagonist for cancer.	PMID:17392428
GANAB		nyulouse	Tes .	Nover	40	,	46.7	0	Impaired proteostasis	31		20	1		•			C.elegans.	NA	No	croup 5	GenAge, synergy Age	PSMC2 is invovled in cell cycle checkpoint during healthy aging.	PMID:17392428
GANAB	s G	nycosyuse	NO	Novel	4/	/	46.7	U		31	1	30	0	9	9	0	Antagonism Not reported	No evidence	NA	NO		-	Target did not associate with any aging hallmarks Aniagonism tor canteer JNK1/2/3 are the upstream of MK3.	
MAPK APK	K. Pro	totein kinase	No	Novel	48	7	46.9	1	Inflammation	26	4	22	4	9	6	3	Antagonism Not reported	No evidence Anti-Longevity: Mycophenolic acid inhibiting IMPDH1 and	NA	Yes	Group 4		While the role of MAPKAPK3/MK3 in aging is unknown, overexpression of MAPK8/JNK in roundworms also increases	
IMPDH1	1 Oxi	idoreductase	Yes	Novel	49	7	47.4	0		15	3	12	0	10	9	1	Antagonism Reported; No effects on lifest	IMPDH2 increased lifespan by 6.08% in	Antagonism	No		DrugAge	Target did not associate with any aging halfmarks	PMID: 33008901
PPP4C	1	Esterase	No	Novel	50	7	48.7	4	Cellular senescence, Epigenetic shift, Genomic	25	4	21	1	9	9	0	Antagonism Reported; reduced lifespan o	by Pro-Longeviry: RNAi PP4-1 decreased lifestan in Drosophila.	NA	Yes	Group 3	-	Antagonist for cancer. PPP4C is involved in DNA double-strand break repair during healthy	
RHOH		Underland	N-	Neural	0	2	50.4	2	instability, Inflammation Epigenetic shift, Genomic	10				-		2	Antagonism Not reported	Not reported	NA	Yes	Group 4		aging. Tumor suppressor gene	PMID: 34452932
PPP1CB		Esterase	No	Novel	52	7	53.9	0	instability, Inflammation	15	5	10	4	7	2	5	Antagonism [*] Not reported	Not reported No evidence	NA	No	-	-	Target did not associate with any aging hallmarks	
ADGRE5	5	GPCR	No	Novel	53	7	55.6	2	Altered intercellular	10	1	9	0	8	4	4	Antagonism Not reported	No evidence	NA	Ves	Group 4		Antagonist for cancer.	
									communications, Inflammation									Pro-Longevity:					ADGRE5 is invovled in innate immune system during healthy aging.	
PSMA5	5 P	Peptidase	Yes	Novel	54	7	57.0	1	Impaired proteostasis Altered intercellular	26	0	26	1	9	8	1	Antagonism Reported; Reduced lifespan of	nlj pas-5 RNAi decreased lifespan by 34.78% in C. elerans .	NA	Yes	Group 3		Antagonist for cancer. PSMA5 is invovled in cell cycle checkpoint during healthy aging. Adipocyte-specific deletion of PIP5K1c reduces diet-induced obesity	PMID:17392428
PIP5K1C	C Non-p	-protein kinase	No	Novel	55	7	57.6	3	communications, Cellular senescence, Deregulated nutrient signaling Altered intercellular	17	2	15	2	8	3	5	Antagonism* Not reported	No evidence	NA	Yes	Group 4		and insulin resistance by increasing energy expenditure Loss of PipSklc in mesenchymal stem cells leads to osteopenia by impairing bone remodeling	PMID: 34996482, PMID: 35090892
ITGB6	F	Receptor	Yes	Novel	56	7	61.7	4	communications, Extracellular matrix stiffness, Genomic instability, Inflammation	11	3	8	3	6	4	2	Antagonism Reported; reduced lifespan o	Pro-Longevity: ily Post-developmental RNAi of pat-3 shortens lifespan of wild type <i>C. elegans</i> .	NA	Yes	Group 3	GenAge	Antagonist for cancer. Our data showd ΠGB6 upregulation in cancer. ΠGB6 is a TGF-β activator. TGF-β signaling was shown to repress body size as well as lifespan <i>in vivo</i> .	PMID: 29070608, PMID: 23144747
S1PR1		GPCR	Yes	Novel	57	7	62.0	0		9	6	3	3	8	0	8	Antagonism* Not reported	No evidence	NA	No			SIPR1 is highly expressed in several tumor types (based on literature). Targeting SIPR1 activity in endothelial cells (ECs) in the setting of anti- VEGFR2 therapy is a potentially attractive strategy to treat VEGFR2 refractory tumors.	
FRK	Tyre	rosine kinase	Yes	Novel	58	7	64.6	1	Inflammation	19	1	18	0	10	8	2	Antagonism Not reported	No evidence	NA	Yes	Group 4		Target did not associate with any aging hallmarks Antagonist for cancer.	
CDC34	1 A.m.	n:hranefarace	No	Noual	50	7	69.7	2	Genomic instability,	14		4	0		6	1	Antagonism Not reported	No evidence	NA	Yes	Group 4		FRK is invovled in innate immune system during healthy aging. Antagonist for cancer.	
		ymanskuse	140	100001	.,			-	Impaired proteostasis			5	0		0	5							CDC34 is involved in adaptive immune system during healthy aging. Upregulation of CSF2RB was found in 3 cancers.	
CSF2RB	B Imm	nunoglobulin	Yes	Novel	60	6	37.3	1	Inflammation	12	3	9	3	6	2	4	Antagonism* Not reported	Not reported Pro-Longevity: VRK1 RNAi decreased lifespan by 36% in C.	NA	Yes	Group 4		Upregulation of CSF2RB may increase the production of Interleukin- 3, Interleukin-5 and GM-CSF, leading to inflammation	
VRK1	Pro	totein kinase	No	Novel	61	6	37.5	1	Cellular senescence	19	1	18	0	10	10	0	Antagonism Reported; Lifespan extensio	 Next revertext accuracy and by 500 mm C. revertext of the second se	Agonism	Yes	Group 2	Age, SynergyAge,pape	Antagonist for cancer.	PMID: 18006689, PMID: 32937443
HLTF	Acy	ryltransferase	No	Novel	62	6	41.7	3	Epigenetic shift, Impaired proteostasis	20	5	15	0	9	9	0	Antagonism Not reported	No evidence	NA	Yes	Group 4	-	Antagonist for cancer, but loss of HLTF function promotes intestinal carcinogenesis	PMID: 22452792
STK26	Pro	otein kinase	No	Novel	63	6	44.7	1	Genomic instability	20	0	20	0	10	7	3	Antagonism Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer, but depletion of STK24 (or MST4) in mice promoted gastric tumorigenesis.	PMID: 32271880
PI4KA	Non-p	-protein kinase	No	Novel	64	6	46.3	0		20	1	19	0	6	2	4	Antagonism* Not reported	No evidence	NA	No			Overexpression of PI4KA is associated with undifferentiated status and poor prognosis of human hepatocellular carcinoma.	PMID: 24393405
PSMC5	н	Hydrolase																		100			Target did not associate with any aging hallmarks	
CPSF3			Yes	Novel	65	6	46.3	1	Impaired proteostasis	19	3	16	1	8	7	1	Antagonism Reported; Reduced lifespan o	Pro-Longevity: n) rpt-6 RNAi decreased lifespan by 38.16% in C.	NA	Yes	Group 3	SynergyAge	Antagonist for cacer.	PMID:17392428
		Esterase	Yes	Novel	65 66	6	46.3 46.7	1	Impaired proteostasis	19 21	3	16 21	1	8	7	1	Antagonism Reported; Reduced lifespan of Antagonism Not reported	Pro-Longevity:	NA NA	Yes		SynergyAge		PMID:17392428
		Esterase	Yes No	Novel	65 66	6		1	Impaired proteostasis	19 21	3 0		1	8 9	7 9	1		Pro-Longevity: ab pro-6 RNAi decreased lifespan by 38.10% in C. devaux. No evidence Anai-Longevity: Dominan-negative mutant increased lifespan by 22% in Drosophile. Constitutively active mutant decreased lifespan by 34% in Drosophile.		Yes No		SynergyAge -	Antagonist for exert PSMCS is involved in cell cycle checkpoint during healthy aging Target did not associate with any aging hallmarks	
RPS6KB2	12 AG	Esterase	Yes No Yes	Novel Novel	65 66 67	6 6		1 0 2	Impaired proteostasis	19 21 12	3 0		1 0 7	8 9 6	7 9 5	1 0	Antagonism Not reported	Pro-Longevity: rpt-6 RNAi decreased lifespan by 38.16% in C. elevans. No evidence Anti-Longevity: Dominant-negative mutati increased lifespan by 22% in Doxophila. Constitutively active mutati decreased lifespan by	NA	Ya No		SynergyAge - GenAge	Ataganin for caser. PSMC5 is involved a cell cycle checkpoint during healthy aging Target di not associate workspoint during healthmack. Attagonist for cancer. Drug urget of MSC-2263118A and LV-278001 investigated in clinical trial (ACTIV91915), SC/C20181878 and NC701115751) for cancer treatment.	PMID: 17392428 PMID: 15186745, PMID: 15186745, PMID: 17266680
	12 AG		Yes No Yes	Novel Novel		6	46.7 47.3	1 0 2	Impaired proteostasis, Telomere attribus	21	3	21	1 0 7	8 9 6	-	1	Antagonism Not reported Antagonism Reported. Lifeopan extensis	Pos-Longoviy; pro-6 RNA decreased lifegin by 38.10% in C. Nord-Congrey); Nord-Congrey); Nord-Congrey); Dominant-enginety mutat increased lifegin by 20% in Drosophila. Constitutively active numatar decreased lifegin by RNA materirence robeing 55% (Inck-) mRNA Cologonic Dietection of the state of the state Cologonic Dietection of the state of the state Na Cologonic Dietection of the state of the state background, induction of the life to a further extension of 40% in maximum lifegina.	NA Antagonism	Ϋ́α	Group 3 Group 1	GenAge	Ataganish for caser PSMC is involved in cell cycle checkpoint during healthy aging Target did not associate the choice of the case of the	PMID: 15186745, PMID: 17266679, PMID: 17266680
RPS6KB2 CTSV	12 A4		Yes No Yes	Novel Novel Novel	65 66 67	6	46.7	1 0 2 3	Impaired proteostasis, Telomere attrition	21	3 0 1	21	1 0 7	8 9 6	7 9 5	1	Antagonism Not reported	Pos-Lengevity: pto 6 RNA decreased likepan by 38.10% in C Norbics Norbics Norbics 20% in Decomposition 20% in Decomposition 20% in Decomposition RNA materimese rubeing 55% (Incl.) IntRNA Posterbard you to result of the second line of the cologones. Decide second on materia do longer. RNA method in 25% successor Response to form body cologones. The second line of the second line of the body cologones. The second line of the second line of the body cologones. The second line of the second line of the second line of the body cologones. The second line of the second	NA	No	Group 3	GenAge	Anagamin for care. PSMCs is nucleot and car clock checkpoint units phashly aging Target did not associate with any aging hallmarks Managamin for target: Managamin for target: Managamin for cancer. A CMS promotes bladder cancer progression, and our data showed in spongations in cancer. CTSM is nucleot and showed in spongation in cancer. Managamin for cancer. CTSM promotes bladder cancer progression, and our data showed in spongations in cancer. CTSM is nucleot and showed in spongation in cancer. Managamin for cancer. Fubicneous suggest antagesis for cancer tenser. (1) sumo-based for the state of the state of the state of the state inperventent in advancer antagesis for cancer tenser. (1) sumo-based por end and word SEI downing Mark Hower and provide our data howed for state of the SEI downing Mark Hower for the state.	PMD: 15160745, PMD: 1226679, PMD: 1226680 PMD: 35443863
	P		Yes No Yes No	Novel Novel Novel		6 6 6	46.7 47.3	1 0 2 3 1	Impaired proteostasis, Telomere attribus	21	3 0 1 2 7	21	1 0 7 0	8 9 10	-	1	Antagonism Not reported Antagonism Reported. Lifeopan extensis	Pos-Longoviy; pro-6 RNA decreased lifegin by 38.10% in C. Nord-Congrey); Nord-Congrey); Nord-Congrey); Dominant-enginety mutat increased lifegin by 20% in Drosophila. Constitutively active numatar decreased lifegin by RNA materirence robeing 55% (Inck-) mRNA Cologonic Dietection of the state of the state Cologonic Dietection of the state of the state Na Cologonic Dietection of the state of the state background, historia of failed to a further extension of 40% in maximum lifegina.	NA Antagonism	Ϋ́α	Group 3 Group 1	GenAge	Anagamin for care: PSRCs is nucleot and care dyce declaption during healthy aging Target did not associate with any aging hallmark: Mangamin for target: Mangamin for target: Mangamin for cancer - (TSV promotes bladder cancer progression, direct and (NCH19971515), NCT200001 investigated in direct and and there of the approximation of the approximation of our data theored in support and and NCT01115731) for cancer transmost. Mangamin for cancer - (TSV promotes bladder cancer progression, and our data theored in support and another formation and our data theored in support and another formation and our data theored in support and another formation and our data theored in support and another formation (TSV is nuclearly and manging KSRI difference) much howed in market (1) sump-based work display and theorem and the 1n - invest, display our data theorem and its construct of the 1n - invest, display our data theorem and its construct of RevV21 data to indee p53, p174047, p140476, and p1510566 prepresents in ASC-1 program and another of the 1000000000000000000000000000000000000	PMID: 15186745, PMID: 17266679, PMID: 17266680
CTSV	P	AGC kinase Peptidase	No	Novel Novel Novel Novel		6 6 6 6	46.7 47.3 50.0 50.2 52.8	3	Impaired proteostasis, Telemere attrices Suffices, Inspired proteostasis, Inflammation	21 12 12 14	2	21 11 10 7	1 0 7 0 3	6	9	1 5	Antagonium Not reported Antagonium Reported, Lifeopun extensis Antagonium Not reported Antagonium Not reported Antagonium Not reported	Po-Lengwi the Application of Book and Application of Book and Applications of Book and Applications of Book and Applications of Applications	NA Antagonism NA NA	No Yes	Group 1 Group 1 Group 4 Group 4	GenAge	Anaganita for care: PSRCs in novelet and coycle checkpourd and phashiby aging Target did not associate with any agine hallmarks Marganita for cancer: Marganita for cancer: Marganita for cancer: Marganita for cancer: Carlos and Marganita for cancer: Marganita for cancer: Carlos and Marganita for cancer: Marganita for cancer: Carlos and Marganita for cancer: Marganita for can	PMD: 1510545, PMD: 1726659, PMD: 1726680 PMD: 35443803 PMD: 35443803 PMD: 1525401, PMD: 1235401, PMD: 1235401,
CTSV KSR1	P	AGC kinase Peptidase sine kinase-like	No	Novel Novel Novel Novel Novel		6 6 6 6 6	46.7 47.3 50.0	3	Impaired protostasis, Telestere strates Estracellular matrix stiffness, Impaired protostasis, Inflammation	21 12 12	2	21 11 10	1 0 7 0 3 1	6	9	1 5	Antagonium Not reported Antagonium Reported, Lifeopun extensis Antagonium Not reported Antagonium Not reported Antagonium Not reported	Po-Lengwir: 9. po-6 RNAdecurand life up with a m C. 10. workine 10. Source of the second life up with a more 1	NA Antagonism NA NA	No Yes Yes	Group 1 Group 1 Group 4	GenAge	Anagamin for case: PGCS is movided and cojeck decident during hunking sing Target dia net associate with any axing hullmarks: Managamin for anxer: Managamin for anxer: Case of the state of the state of the state of the state discretion of the state of the state of the state discretion of the state of the state of the state Managamin for anxer: CTSV promotes builder cancer progression, and our data showed in spongalitation in anxer: (CTSV as novbed) in anticeminant system of the state and our data showed in spongalitation in anxer: (CTSV as novbed) in antieminant system, and system and our data showed in spongalitation in anxer: (CTSV as novbed) in antieminant system, and state and collabor the state state of the state state (CTSV as novbed) in antieminant system, and state for any state state state state of the state state (CTSV as novbed) in antieminant system, and state states (CTSV as novbed) in antieminant system, and states (CTSV as novbed) in a state states and states and states (CTSV as novbed) in a state states and states and states (CTSV as novbed) in any states and states and states (CTSV as novbed) in a state states and states and states (CTSV as novbed) in a state states and states and states (CTSV as novbed) in a state state states	PMD: 1538755, PMD: 1726659, PMD: 1726680 PMD: 3543863
CTSV KSR1	P Tyrosi 6 Acy	AGC kinase Peptidase sine kinase-like	No	Novel Novel Novel Novel Novel Novel		6 6 6 6 6 6 6	46.7 47.3 50.0 50.2 52.8	3	Impared protestasis, Tchenere attrices Estracellular matrix stiffness, impared protestasis Impared protestasis Impared protestasis	21 12 12 14	2	21 11 10 7	1 0 7 0 3 3 1 1	6 8 8	9 1 6 8	1 5 2 0	Antagonium Not reported Antagonium Reported, Lifeopan extension Antagonium Not reported Antagonium Not reported Antagonium Not reported	Po-Lengery: gr of SUSTAINSTAINSTAINSTAINSTAINSTAINSTAINSTAIN	NA Antagonism NA NA	No Yes Yes	Group 1 Group 1 Group 4 Group 4	GenAge	Anggenin for case: PSGS is movided and cojeck headpoint with publicly ang Target din net associate with any axies hallmark: Margenin for cases: Margenin	PMD: 1518/545, PMD: 1726659, PMD: 1726680 PMD: 3543863 PMD: 3543863 PMD: 1554801, PMD: 1557801,

DX39A	Hydrolase	No	Novel	73	6	58.8	0		12	8	4	0	11	11	0	Antagonism Reported; Reduced lifespar	Hel-1 downregulation resulted in a 9.3% decrease in Integram compared to wild type in C. elegans . This effect was even more prosounced in daf-2 mutants which showed a 26.9% decrease in Integram. The results suggested that hel-1 promoted longevity	NA	No		GenAge	Target did not associate with any aging hallmarks	PMID: 2619574
Z1B	yrosine kinase	No	Novel	74	6	64.0	2	Cellular senescence, Epigenetic shift	24	3	21	0	9	9	0	Antagonism Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. BAZ1B is invovled in DNA double-strand break repair during healthy aging.	
	Protein kinase	No	Novel	75	6	70.3	1	Genomic instability	20	1	19	0	11	11	0	Antagonism Not reported	No evidence	NA	Yes	Group 4			
	Hydrolase	No	Novel	76	6	71.0	3	Epigenetic shift, Genomic instability, Inflammation Altered intercellular	26	0	26	0	10	8	2	Antagonism Reported; Reduced lifespar	only Pro-Longevity: apy-1 RNAi decreased lifespan in C. elegans .	NA	Yes	Group 3	GenAge	Antagonist for cancer. CANT1 is invovled in innate immune system during healthy aging.	PMID: 1821628
	cyltransferase	No	Novel	77	6	72.7	3	communications, Genomic instability, Impaired proteostasis	17	0	17	1	10	10	0	Antagonism Not reported	No evidence	NA	Yes	Group 4		Tumor suppressor gene	
																						Our data showed downregulation in cancer, suggesting agonist for cancer treatment.	
	CMGC kinase	No	Novel	78	5	28.8	3	Altered intercellular communications, Cellular senescence, Genomic instability	18	1	17	0	8	2	6	Antagonism* Reported; Reduced lifespar	Pro-Longevity: only hpk-1 RNAi decreased lifespan by 35% in C. elegans .	NA	Yes	Group 3	GenAge	However, oncogenically transformed HIPK1 -/- mouse embryonic fibroblasts were more susceptible than transformed HIPK1 +/- cells to apoptosis induced by DNA damage, and carcinogen-treated HIPK1 -/- mice developed fewer and smaller skin tumors, than HIPK1 mice.	PMID: 2367621 PMID: 1270276 PMID: 1800668
	Peptidase	Yes	Novel	79	5	34.0	1	Impaired proteostasis	20	0	20	1	10	8	2	Antagonism Not reported	No evidence	NA	Yes	Group 4		HIPK1 drives p53 activation to limit colorectal cancer cell growth Antagonist for cacer. PSMA2 is invoved in cell cycle checkpoint during healthy aging	
		v		~	,	~ .		Altered intercellular communications, Epigenetic shift, Genomic	17													LB-100, PPP2CB inhibitor, was investigated for the treatment of glioblastoma and oligodendroglioma (phase II). LB-100 targets PPP2CB, PPP2C and PPP2CA. LB-100 exhibits anti- cancer activity via its chemo- and radio-sensitizing properties.	PMID: 258978
	Esterase	Yes	Novel	80	3	36.4	6	instability, Impaired proteostasis, Inflammation, Mitochondrial dysfunction	17	3	14	6	9	I	8	Antagonism* Reported; reduced lifespan	et 92 RNAi decrensed lifespan in C. elegans .	NA	Yes	Group 3		However, our data showed downregulation in PPP2CB in cancer was inconsistent with the evidence that inhiting PPP2CB exhibits ati- cancer activities Besides, PPP2CB is important for cell cycle checkpoint and adaptive immune system during healthy aging.	PMID: 333158
	Protein kinase	No	Novel	81	5	38.2	1	Impaired proteostasis	12	9	3	0	9	6	3	Antagonism Reported; reduced lifespan	aux KNAi decreased ittespan in Drosophila.	NA	Yes	Group 3		Antagonist for cancer. GAK knockdown by siRNA decreased cell proliferation in osteosarcoma. GAK ablation in mice causes kidnev failure due to caloain activation	PMID: 208812 PMID: 332085 PMID: 281472
	yrosine kinase	Yes	Novel	82	5	40.8	3	Extracellular matrix stiffness, Inflammation, Stem cell exhaustion	8	5	3	1	9	5	4	Antagonism* Reported; Reduced lifespar	Pro-Longevity: btk29a ficP null mutation decreased lifespan in Orazophila. Btk29A is the sole Tee family member in Droizophila.	NA	Yes	Group 3		TEC kinase stabilized PLK4 to promote liver cancer metastasis.	PMID: 160231 PMID: 346378
	cyltransferase	No	Novel	83	5	44.8	I	Impaired proteostasis	18	2	16	0	8	8	0	Antagonism Not reported	No evidence	NA	Yes	Group 4		UBA2 is a heterodimer, acting as an E1 ligase for SUMO1, SUMO2, SUMO3, and probably SUMO4. Antagonitis for encer. UBA2 could promote cell migration and invasion through WarH-statenin signaling in gastric cancer. UBA2 knockdown and inhibiting SAE1/UBA2-mediated SUMOylation resulted in reduced glycolysis.	PMID: 30479 PMID: 28088 PMID: 31788 PMID: 32938
	Hadrolase				,	53.4	,	Impaired proteostasis,	24		24					Antagonism Not reported		NA	Yes			SUMOylation of IkBa has as a strong inhibitory effect on NF-xB- dependent transcription, and SUMOylation of p53 prevents its proteasome degradation.	
	Receptor	No	Novel	84 85	5	58.6	0	Mitochondrial dysfunction	12	2	10	0	8	2	6	Antagonism Not reported	No evidence No evidence	NA	No	Group 4		RAB1B is invovled in cell cycle regulation during healthy aging. Tareet did not associate with any aging hallmarks	
	Peptidase	Yes	Novel	86	5	63.0	1	Impaired proteostasis	18	1	17	1	7	7	0		Pro-Longevity: only phs-2 RNAi decreased lifespan by 31.88% in C.	NA	Yes	Group 3	SynergyAge	Antagonist for cancer.	PMID: 17392
3	ethyltransferase	No	Novel	87	5	65.2	0	- Altered intercellular	15	2	13	0	8	7	1	Antagonism Not reported	elegans. No evidence	NA	No			PSMB7 is involved in cell cycle checkpoint during healthy aging Target did not associate with any aging hallmarks	
	cyltransferase	No	Novel	88	5	76.8	5	communications, Epigenetic shift, Genomic instability, Impaired	29	1	28	0	8	8	0	Antagonism Not reported	No evidence	NA	Yes	Group 4	-	Antagonist for cancer. TRIM37 is involved in adaptive immune system during healthy aging.	
	txidoreductase	No	Novel	89	4	23.3	3	proteostasis, Inflammation Deregulated nutrient signaling, Epigenetic shift, Mitochondrial dysfunction	9	1	8	0	8	8	0	Antagonism Reported; Lifespan exten	Pro-Longevity: Ubiquitous Nmdme overexpression increased lifespan by 20% in Drosophila. Nmdme fut body specific overexpression increased lifespan by 23% in male Drosophila and 14% in female Drosophila.	Agonism	Yes	Group 2	GenAge	Antagonist for cancer. MTHFD2 is involved in metabolism of water-soluble vitamins and cofactors during healthy aging	PMID: 26319
	Protein kinase	No	Novel	90	4	41.3	2	Cellular senescence, Genomic instability	23	2	21	2	6	5	I	Antagonism Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. TAOK1 is invoved for cell cycle checkpoints during healthy aging Antagonism canosismi depends on cancer types. Inconsistent dysregulation (upregulate and downregulate) in different cancers. ARL2 inhibits the proliferation, migration and tumorigenicity of gloma cells.	PMID: 29843
	Hydrolase	No	Novel	91	4	49.5	1	Mitochondrial dysfunction	13	4	9	0	9	4	5	Antagonism Not reported	No evidence	NA	Yes	Group 4		ARL2 was first reported to behave as a tumor suppressor in breast cmccr. In contrast, miR-214 down-regulates ARL2 and suppresses growth and invasion of cervical cancer cells. ARL2 is required for homologous recombination repair in colon cancer stem cells.	PMID: 32426 PMID: 28137 PMID: 35567
	Hydrolase	No	Novel	92	4	50.5	0	Cellular senescence.	12	2	10	0	9	9	0	Antagonism Not reported	No evidence	NA	No			Target did not associate with any aging hallmarks	
N	n-protein kinase	No	Novel	93	4	50.8	3	Deregulated nutrient signaling, Extracellular matrix stiffness Altered intercellular communications, Cellular	9	3	6	1	9	9	0	Antagonism Not reported	No evidence Pro-Longevity:	NA	Yes	Group 4			
	cyltransferase.	No	Novel	94	4	53.0	7	communications, Centular senescence, Deregulated nutrient signaling, Epigenetic shift, Genomic instability, Impaired proteostasis, Inflammation	31	3	28	0	5	3	2	Antagonism* Reported; Reduced lifespar	The average lifespan of Clock-/- mice is reduced by	NA	Yes	Group 3	GenAge	Age-related changes of clock gene expression promote declining autophagy levels	PMID: 2114 PMID: 27574 PMID: 2156
	Hydrolase	Yes	Novel	95	4	55.0	1	Impaired proteostasis	30	0	30	0	10	9	1	Antagonism Not reported	No evidence	NA	Yes	Group 4	-	Antagonist for cacer. PSMC1 is invovled in cell cycle checkpoint during healthy aging	
	Peptidase	No	Novel	96	4	56.3	1	Impaired proteostasis	14	9	5	0	11	6	5	Antagonism Not reported	No evidence	NA	Yes	Group 4		Antagonist for cancer. USP11 is involved in regulating p53 stability by deubiquitinating p53.	PMID: 25471
	Peptidase	Yes	Novel	97	4	56.8	1	Impaired proteostasis	12	1	11	1	6	6	0	Antagonism Reported; No effects on life	spar No evidence on modulating longevity: pbs-6 RNAi did not change lifespan in C. elegans.	NA	Yes	Group 4	SynergyAge	Antagonist for cacer. PSMB1 is involved in cell cycle checkpoint during healthy aging	PMID: 173924
G	cosyltransferase	No	Novel	98	4	57.0	0	- Cellular senescence,	20	0	20	0	8	7	1	Antagonism Not reported	No evidence	NA	No			Tareet did not associate with any against hallmarks p90RSK inhibitor, TAS0612, was investigated for neoplasm in phase I trial, but our data showed downregulation of RPS6KA6 in cancers. Dataletion of 56L1 meetikes non-expression proteines of endoris	
	AGC kinase	Yes	Novel	99	4	57.5	4	Genomic instability, Impaired proteostasis, Mitochondrial dysfunction	19	5	14	2	8	2	6	Antagonism* Not reported	No evidence	NA	Yes	Group 4		restriction or prolongs lifespan by pharmacological activation of AMPK in mice. AMPK in mice. AMPK in the set of the set	PMID: 197976 PMID: 224934 PMID: 153068
	cyltransferase	No	Novel	100	4	59.3	2	Impaired proteostasis, Inflammation	7	3	4	0	8	2	6	Antagonism* Not reported	No evidence	NA	Yes	Group 4		Knockdown of HERCS significantly induced the expression of p33, p21 and Bax/Bcl-2 in HCC cells, resulting in apoptosis augment. HERCS was over-expressed in both HCC tissue samples and cell	PMID: 289195

Group-4 targets[1]	Clinical trial status	Novelty	Occurence in any overlapped biological processes[2]	Therapeutic approach for cancer treatment[3]	Predicted therapeutic approach for healthy anti-aging	Potential dual purpose candidatess	l- Role in healthy aging	References
ADRA2C	Yes	Novel	\checkmark	Agonism	Agonism	\checkmark	Guanfacine hydrochloride agonisting ADRA2A, ADRA2B and ADRA2C extended lifepan in C. elegans.	PMID: 24134630
AKT3	Yes	HC	\checkmark	Antagonism*	Antagonism	\checkmark	Aging-induced Akt activation involves in aging-related pathologies and Aβ-induced toxicity	PMID: 31183966
CSF2RB	Yes	Novel	\checkmark	Antagonism*	Antagonism	\checkmark	Upregulation of CSF2RB may increase the production of Interleukin-3, Interleukin-5 and GM-CSF, leading to inflammation	-
FASN	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	FANS inhibitor prevented the initiation of senescence induction in hematopoietic stem cells and reduced the effect of the activation of senescence on different age-associated diseases. DEHP/DEP (increasing fasn-1 expression, and affecting other lipid metabolic genes) treated C. elegans lifespan decreased.	PMID: 30962418, PMID: 29020644
FGR	Yes	Novel	\checkmark	Antagonism*	Antagonism	\checkmark	FGR inhibitor, such as dasatinib was investigated for cancer, although our data showed FGR downregulation in cancers. Dasatinib and quercetin restore α-Klotho in mice and humans, which may amplify protection against aging and age-related diseases.	PMID: 35292270
HCK	Yes	Novel	\checkmark	Antagonism	Antagonism	\checkmark	Constitutive activation of the SRC family kinase Hck results in spontaneous pulmonary inflammation and an enhanced innate immune response.	PMID: 12208875
HDAC2	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	Inactivating histone deacetylase HDA promotes longevity by mobilizing trehalose metabolism. HMGB1 mediates neuroinflammatory priming in the aged brain.	PMID: 33790287 PMID: 30988279.
HMGB1	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	Blocking the actions of HMGB1 appears to "desensitize" aged microglia to an immune challenge, thereby preventing exaggerated behavioral and neuroinflammatory responses following infection	PMID: 27466339
IL1B	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	IL-1 α and IL-1 β signal upregulate the senescence-associated secretory phenotype in a cooperative manner. IL-1 β promotes the age-associated decline of beta cell function	PMID: 30988157, PMID: 34746709
							ITGB5 served as a ligand for Cyr61, a molecule stimulating the production of IL-6, which is	PMID: 32064162,
ITGAV	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	considered an aging biomarker, via itgav/itgb5/Att/NF-KB signaling pathway in rheumatoid arthritis	PMID: 17071038,
KDM1A	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	KDM1A, is a drug target of IMG-7289, lysine-specific demethylase 1 inhibitor, investigated for the treatment of leukemia in trial (NCT02842827). Modulation of KDM1A with validemstat (KDM1A inhibitor) rescues memory deficit and behavioral alterations in mice	PMID: 22547695 PMID: 32469975
KDM2A	No	Novel	\checkmark	Antagonism	Antagonism	\checkmark	KDM2A deficiency in macrophages enhances thermogenesis to protect mice against HFD-induced obesity.	PMID: 27029061, PMID: 33462408
KRAS	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	Genetic inhibition of Ras was found to extend lifespan. Adult-onset administration of the drug trametinib inhibiting MAP2K1 and MAP2K2, a highly specific inhibitor of Ras-Erk-ETS signaling, extended lifespan in Drosophila.	PMID: 29276789, PMID: 26119340
LYN	Yes	Novel	1	Antagonism	Antagonism	1	Autorouse administration of the drug function of motion grant 2x1 and WAT2K2, a night specific miniotor of Ras-LTA-LT3 signaling, extended mespan in <i>Drosophila</i> . Uns suppressess osteoclassicoenesis in vitro and in vitro.	PMID: 19171907
MET	Yes	HC	1	Antagonism	Antagonism	~	Lyn suppress osciolastogenesis in vito and in vivo. MET activates RAS and AKT signaling.	PMID: 28677234
				-			Aging is associated with increased matrix metalloproteinase-2 activity in the human aorta	
MMP2	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	MMP2 was considered as classsical senescence-associated secretory phenotype (SASP).	PMID: 15831360
MST1R	Yes	Novel	\checkmark	Antagonism	Antagonism	\checkmark	MST1R inhbito prevents bone osteolysis.	PMID: 30967626, PMID: 28248933
RARA	Yes	HC	\checkmark	Agonism	Agonism	\checkmark	RAR agonist ameliorated the UV-induced damage to skin collagen fibers, and increased the collagen content in photoaged skin through RAR.	PMID: 28849147
RARB	Yes	HC	1	Agonism	Agonism	~	RAR agonist ameliorated the UV-induced damage to skin collagen fibers, and increased the collagen content in photoaged skin through RAR.	PMID: 28849147
RPS6KA2	Yes	Novel	\checkmark	Antagonism*	Antagonism	\checkmark	Involved PI3K/AKT/MTOR signaling	-
RPS6KA4	No	Novel	\checkmark	Antagonism	Antagonism	\checkmark	Depletion of S6k1 resembles gene expression patterns of caloric restriction or prolongs lifespan by pharmacological activation of AMPK in mice.	PMID: 35232347, PMID: 19797661
RPS6KA6	Yes	Novel	\checkmark	Antagonism*	Antagonism	\checkmark	Depletion of S6k1 resembles gene expression patterns of caloric restriction or prolongs lifespan by pharmacological activation of AMPK in mice. S6K1 regulates glucose metabolism via feedback regulation of insulin receptor substrate 1 to improve glucose tolerance and insulin sensitivity in liver-specific and systematic S6k1- deficient mice.	PMID: 19797661, PMID: 22493495, PMID: 15306821
SRC	Yes	HC	\checkmark	Antagonism	Antagonism	\checkmark	Dasatinib targeting SRC was considered as senolytic used to remove senescent cell.	-
ABL1	Yes	HC	\checkmark	Antagonism	Not suitable for antagonsim	x	ABL1 is important for DNA double-strand break repair during healthy aging. Senolytic treatment reduces cell senescence. Quercetin, senolytic drug, inhibits multiple kinases including ABL1.	PMID: 3201088
ADGRE5	No	Novel	~	Antagonism	Not suitable for	x	Imatinib mesylate inhibiting ABL1 reduced lifespan in <i>C. elegans</i> . ADGRE5 is invovled in innate immune system during healthy aging.	Reactome
ANAPC2	No	Novel	~	Antagonism	antagonsim Not suitable for	x	ANAPC2 is involved in cell cycle checkpoint during healthy aging.	PMID: 21191042
AURKA	Yes	HC	1	Antagonism	antagonsim Not suitable for	x	The anaphase promoting complex is required for memory function in mice AURKA is involved in cell cycle regulation during healthy aging	Reactome
AURKB	Yes	HC	1	Antagonism	antagonsim Not suitable for	x	AURKA is involved in cell cycle checkpoing during healthy aging	Reactome
BAZ1B	No	Novel	√	Antagonism	antagonsim Not suitable for	x	BAZIB is involved in DNA double-strand break repair during healthy aging.	Reactome
BLK	Yes	Novel	√ √	Antagonism*	antagonsim Conditional	x	BAZIB is invovied in DNA double-strand break repair during nearing aging. BLK is a pro-senescence kinase.	PMID: 26583757
				0	Not suitable for			
CDC34	No	Novel	√	Antagonism	antagonsim Not suitable for	х	CDC34 is involved in adaptive immune system during healthy aging.	Reactome
CDK6	Yes	HC	\checkmark	Antagonism	antagonsim Conditional	х	CDK6 is involved in cell cycle regulation during healthy aging CXCR4 gene deletion in young mesenchymal stem cells accelerates an aging phenotype including increased production of reactive oxygen species, DNA damage, senescence, and	Reactome
CXCR4	Yes	HC	\checkmark	Antagonism	(Agonism for young, Antagonism for old)	х	CACKA gene detection in young mesenenymai stem cens accelerates an aging pnenotype including increased production of reactive oxygen species, DNA damage, senescence, and reduced proliferation. In constrast, CXCL12/CXCR4 promotes inflammation. Targeting CXCR4 for antiaging may be suitable for aged adults only.	PMID: 26848769, PMID: 32418119

DNM2	No	HC	\checkmark	Antagonism	Not suitable for antagonsim	x	Tumor suppressor gene	
DNMT1	Yes	HC	\checkmark	Antagonism	Agonism	x	DNMT1 maintains genomic methylation stabiluty and insufficient DNA methylation affects healthy aging and promotes age-related health problems	PMID: 22704347,
DNMT3A	Yes	HC	\checkmark	Antagonism	Agonism	x	No difference in longevity was observed between Dnmt1-deficient mice and normal controls. Constitutive loss of DNMT3A causes morbid obesity through misregulation of adipogenesis	PMID: 16510855 PMID: 35635747
DNMT3B	No	HC	\checkmark	Antagonism	Agonism	x	DNMT3B plays a protective role against hepatocarcinogenesis caused by chronic inflammation via maintaining mitochondrial homeostasis.	PMID: 33221743, PMID: 33277576
FES	No	Novel	\checkmark	Antagonism*	Not suitable for antagonsim	х	FES kinase activity is also dispensable for hematopoiesis.	PMID: 322556211, PMID: 10523632
					Not suitable for		FGF2 (or bFGF) is neuroprotective for healthy aging.	
FGF2	Yes	HC	\checkmark	Antagonism*	antagonsim	х	It can improve motor function recovery, increase tyrosine hydroxylase positive neuron survival, and upregulate the levels of neurotransmitters in the brain of a rat model of Parkinson's disease.	PMID: 30274251
FGFR1	Yes	HC	\checkmark	Antagonism*	Not suitable for antagonsim	x	Mice with an attenuation of FGFR1 signalling develop diabetes with age and exhibit a decreased number of beta-cells, and lower levels of FGFR1 in mice have also been related to craniofacial defects.	PMID: 12514106, PMID: 11130726
FGFR2	Yes	HC	\checkmark	Antagonism*	Not suitable for antagonsim	х	FGFR2 is important for cell division, cell maturation, formation of new blood vessels, wound healing, and bone growth and development	-
FRK	Yes	Novel	\checkmark	Antagonism	Not suitable for antagonsim	x	FRK is invovled in innate immune system during healthy aging.	Reactome
HLTF	No	Novel	\checkmark	Antagonism	Not suitable for antagonsim	x	Loss of HLTF function promotes intestinal carcinogenesis	PMID: 22452792
							ITK is important for adaptive immune system during healthy aging.	
ITK	Yes	Novel	\checkmark	Antagonism	Not suitable for antagonsim	х	btk29a ficP null mutation decreased lifespan in Drosophila.	PMID: 23672610, PMID: 16023106
					c		Btk29A is the sole Tee family member in <i>Drosophila</i> , including itk.	
							KAT6A belongs to histone acetyltransferase (HAT). Stability of HATs and histone deacetylases activities is necessary to maintain normal cellular functions or otherwise leads to	PMID: 19818845,
KAT6A	No	Novel	\checkmark	Antagonism	Agonism	х	aging. KAT6A was found to regulate Nrf2/ARE signaling pathway and inhibit ROS accumulation in bone marrow-derived mesenchymal stem cells from the old, thus promoting proliferation, colony formation, and osteogenic differentiation of OBMSCs. KAT6A could promote osteogenesis of OBMSCs.	PMID: 33541408, PMID: 34808502
KDR	Yes	HC	1	Antagonism*	Not suitable for	x	KDR antagonists such as Ramucirumab, Cabozantinib approved for cancer treatment but our data showed KDR downregulation in cancers.	
KIT		НС	,	-	antagonsim		KDR may be needed for normal angiogenesis, to ensure developing or healing tissues receive an adequate supply of nutrients. Adult myocardium relies on c-kit expression to regenerate after injury and to counteract aging effects on cardiac structure and function.	PMID: 31275242,
KII	Yes	пс	v	Antagonism*	Agonism	х	Imatinib mesylate inhibiting PDGFRB, ABL1, KIT, BCR reduced lifespan in <i>C. elegans</i> . KSP1 is positively regulate MAPK signaling in the context of constitutively active RAS. Genetic inhibition of Ras was found to extend lifespan.	PMID: 32010883
KSR1	No	Novel	\checkmark	Antagonism*	Agonsim	x	RasV12 failed to induce p53, p19ARF, p16INK4a, and p15INK4b expression in KSR1-/- primary mouse embryo fibroblasts and increased proliferation instead of causing growth	PMID: 29596465, PMID: 12874031,
				-	-		arrest. Reintroduction of wild-type KSR1 rescued RasV12-induced senescence.	PMID: 16507997
MAPKAPK3	No	Novel	\checkmark	Antagonism	Agonism	x	JNK1/2/3 are the upstream of MK3. While the role of MAPKAPK3/MK3 in aging is unknown, overexpression of MAPK8/JNK in roundworms also increases lifespan.	-
MAPKAPK5	Yes	Novel	\checkmark	Antagonism	Not suitable for antagonsim	х	MAPKAPK5 is considered as tumor suppressor serine/threonine-protein kinase involved in mTORC1 signaling.	
MCM8	No	Novel	\checkmark	Antagonism	Not suitable for	x	MCM8 is involved in cell cycle checkpoint and DNA replication during healthy aging.	Reactome
				U	antagonsim Not suitable for		MDM2 is a negative regulator of p53, a tumor-suppressor gene. Dominant-negative versions of Drosophila melanogaster p53 in adult neurons extends lifespan.	
MDM2	Yes	HC	\checkmark	Antagonism	antagonsim	х	Taken together, antagonizing MDM2 may result in increased p53 activities, which in turn contribute to accelerated aging. However, small-molecule MDM2 antagonists attenuate the senescence-associated secretory phenotype.	-
							Aging or ER antagonists were shown to downregulate NCOA1 in the hippocampus of female mice. 17β-estradiol treatment can upregulate NCOA1. Beta-Estradiol was shown to increase lifespan in <i>C. elegans</i> .	PMID: 26287601,
NCOA1	No	HC	\checkmark	Antagonism*	Agonism	х	Taken together, NOCA1 agonist may delay aging.	PMID: 24134630
							NCOA1 is required for the anti-obesogenic effects of 17β-estradiol. NCOA3 overexpression is required in order to maintain the telomerase activity.	
NCOA3	No	HC	\checkmark	Antagonism	Agonism	х	NCOA3 is an inhibitor of senescence whose downregulation in aged individuals could be probably a tumor suppressor mechanism, preventing the clonal expansion of risky old cells from having damaged DNA.	PMID: 26469953
NR3C1	Yes	HC	\checkmark	Agonism	Antagonism Not suitable for	х	Cyproterone acetate inhibiting AR, PGR & NR3C1 (approved for human use) extended lifespan in C. elegans . PDGFR-β signaling in the cardiomyocyte may regulate angiogenesis in the heart in response to load-induced stress through several different mechanisms.	PMID: 24134630 PMID: 20071776,
PDGFRB	Yes	HC	\checkmark	Antagonism	antagonsim	х	Imatinib mesylate inhibiting PDGFRB, ABL1, KIT, BCR reduced lifespan in <i>C. elegans</i> .	PMID: 20071770, PMID: 3201088
РКМ	No	HC	\checkmark	Antagonism	Not suitable for antagonsim	х	PKM is involved in innate immune system during healthy aging. In addition, loss of PKM2 impairs angiogenic sprouting and loss of endothelial PKM2 alters mitochondrial metabolism.	PMID: 30301887
PLK1	Yes	HC	\checkmark	Antagonism	Not suitable for antagonsim	х	PLK1 is involved in cell cycle regulation and DNA checkpoint during healthy aging; PLK1 promotes autophagy.	PMID: 28102733, PMID: 26597721
POLE	Yes	Novel	\checkmark	Antagonism	Not suitable for antagonsim	x	Tumor suppressor gene	-
PPP5C	No	Novel	\checkmark	Antagonism	antagonsim Not suitable for antagonsim	x	PPPSC is invovled in DNA double-strand break repair during healthy aging.	Reactome
					anabononn			

PTK2	Yes	HC	\checkmark	Antagonism	Not suitable for antagonsim	х	PTK2 is involved in innate immune system during healthy aging.	Reactome
RAC1	No	HC	\checkmark	Antagonism	Not suitable for	x	RAC1 is involved in adaptive immune system and innate immune system during healthy aging.	
					antagonsim		RBCK1 depletion increases p53 protein levels and p53 target genes, and	
RBCK1	No	Novel	\checkmark	Antagonism	Not suitable for antagonsim	x	BICK1 theretex with PTEN (tumor suppressor geen) and promotes PTEN degradation in K48-linked ubiquitination. Dominant-negative versions of Drosophila melanogaster p53 in adult neurons extends lifespan.	PMID: 30874541, PMID: 35174471
								https://escholarshi
RHOA	No	HC	\checkmark	Antagonism	Agonism	х	RHOA is invovled in protecting against the progression of cardiac aging.	p.org/uc/item/14g 0843j
BUOU			,		Not suitable for			00401
RHOH	No	Novel	\checkmark	Antagonism	antagonsim	х	Tumor suppressor gene	-
SMARCA4	No	HC	\checkmark	Antagonism	Not suitable for	х	Tumor suppressor gene	
					antagonsim		SMO inhibition promotes aging.	
SMO	V	Name	1	A	Not suitable for		SMO has shown to be critical for the hedgehog signal transduction on the cell membrane. Hedgehog signaling is dysregulated in old hepatocytes, and this accelerates aging.	D. (ID. 24004007
SMO	Yes	Novel	V	Antagonism	antagonsim	х	Deleting SMO in young hepatocytes before partial hepatectomy prevented hedgehog pathway activation after partial hepatectomy and inhibited regeneration.	PMID: 34984806
					N		In addition, hedgehog inhibition promoted telomere shortening and mitochondrial dysfunction in hepatocytes.	
STK26	No	Novel	\checkmark	Antagonism	Not suitable for antagonsim	х	Depletion of STK24 (or MST4) in mice promoted gastric tumorigenesis.	PMID: 32271880
TAOK1	No	Novel	1	Antagonism	Not suitable for	x	TAOK1 is invovled for cell cycle checkpoints during healthy aging	Reactome
TAOKI	140	NOVCI	v	Antagonishi	antagonsim	~		Reactome
							TLR4 is an important Pattern Recognition Receptor (PRR), which activates both innate and adaptive immune cells. Its activation leads to inflammatory cytokine production which is responsible for activating the innate immune system.	
TLR4	Yes	HC	\checkmark	Antagonism*	Conditional	х	its activation reads to initializing of the second strength of the s	PMID: 32508811,
				0			The Toll-like receptor 4 (TLR4) signaling pathway is involved in many aspects of biological functions of AML cells, including the regulation of pro-inflammatory cytokine products,	PMID: 30336978
							myeloid differentiation, and survival of AML cells.	
TNF	Yes	HC	\checkmark	Antagonism	Conditional (Antagonism for old)	х	TNF- α antagonism rescues the effect of ageing on stroke; TNF- α /IFN- γ synergy amplifes senescence-associated inflammation. TNF-deficient mice develop normally but are more susceptible to some infectious agents.	PMID: 34076259, PMID: 35645319
TODA	v	110	,		Not suitable for		TOP2A is involved in cell cycle regulation during healthy aging.	
TOP2A	Yes	HC	\checkmark	Antagonism	antagonsim	х	Topoisomerases regulate the topological states of DNA and important for neuron proliferation.	PMID: 7980433
TRAF7	No	Novel	\checkmark	Antagonism	Not suitable for	х	Tumor suppressor gene	-
					antagonsim Not suitable for			
TRIM37	No	Novel	\checkmark	Antagonism	antagonsim	х	TRIM37 is involved in adaptive immune system during healthy aging.	Reactome
			,				Using bone-targeting recombinant adeno-associated virus 9 (rAAV9) to enhance Bmall or Ttk might have a therapeutic effect on senile osteoporosis and delays bone repair in aging	https://doi.org/10.
TTK	No	Novel	\checkmark	Antagonism	Agonism	х	mice.	<u>1016/j.omtn.2023.</u> 02.014
UBE2C	No	HC	1	A	Not suitable for			
UBE2C	INO	пс	v	Antagonism	antagonsim	х	UBE2C is involved in cell cycle checkpoints during healthy aging	Reactome
UBE2L6	No	Novel	\checkmark	Antagonism	Not suitable for antagonsim	х	UBE2L6 is invovled in adaptive immune system during healthy aging.	Reactome
			,		Not suitable for			
UBE2M	No	Novel	\checkmark	Antagonism	antagonsim	х	UBE2M is invovled in adaptive immune system during healthy aging.	Reactome
VEGFA	Yes	HC	\checkmark	Antagonism	Not suitable for	х	Counteracting age-related VEGF signaling insufficiency promotes healthy aging and extends lifespan.	PMID:34326210
ARL2	No	Novel	-	Antagonism	antagonsim	_		
CTSB	No	HC	_	Antagonism		_		-
CTSV	No	Novel	-	Antagonism	-	-		-
HDAC10	Yes	Novel	-	Antagonism	-	-	-	-
HERC5	No	Novel	-	Antagonism*	-	-	-	-
ITGA9 PIP5K1A	No No	Novel Novel	-	Agonism Antagonism	-	-		
PIP5K1C	No	Novel	-	Antagonism*	-	-	-	-
PRIM1	Yes	Novel	-	Antagonism	-	-		-
PSMA2	Yes	Novel	-	Antagonism	-	-	-	-
PSMA3	Yes	Novel	-	Antagonism	-	-		-
PSMA4 PSMB1	Yes Yes	Novel Novel	-	Antagonism	-	-	-	
PSMB1 PSMB6	Yes	Novel	-	Antagonism Antagonism	-	2		-
PSMC1	Yes	Novel	-	Antagonism	-	-		-
PSMC4	Yes	Novel	-	Antagonism	-	-	-	-
PTPRF	No	Novel	-	Antagonism	-	-		-
RAB1B TOP2B	No Yes	Novel Novel	-	Antagonism Antagonism*	-	-	-	-
UBA2	No	Novel	-	Antagonism [*]	-	2		-
UBE2T	No	Novel	-	Antagonism	-	-		-
USP11	No	Novel	-	Antagonism	-	-	· · · · · · · · · · · · · · · · · · ·	
1] Common cancer targets	s from group 4 (F	Figure 5; Table 5	S6)					

[1] Common cancer targets from group 4 (Figure 5; Table S6)

[2] Any occurrence in the 90 overlapped biological processes enriched with 51 targets (gorup 1 and group 2) contributed to lifespan extension [3] Generally, upregulation in expression leads to proposed antagonist for cancer; downregulation in expression leads to proposed agonist for cancer. * The therapeutic approach is proposed based on target's mechanism of action (see Table S6 for details)

Table S8. Gene Ontology terms commonly enriched by lifespan-extending (Group 1 and Group 2) and Group 4 targets

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00000000000000000000000000000000000	GO:0030335	positive regulation of cell migration	13/101	1.45E-09	1.61E-07	LYN/PTK2/IL1B/KDR/VEGFA/ITGAV/KIT/MMP2/PDGFRB/CXCR4/FGR/SMO/RHOA
0000180 00001810 0000181001014	GO:0016570	histone modification	9/101	2.55E-08	2.06E-06	AURKA/KDM1A/AURKB/NCOA1/PKM/RPS6KA4/KAT6A/BAZ1B/NCOA3
0000180 00001810 0000181001014	GO:0043536	positive regulation of blood vessel endothelial cell migration	6/101	5.85E-08	3.82E-06	KDR/VEGFA/FGF2/HMGB1/FGFR1/AKT3
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0.000559 interchair again conduction 1410 2.1247 9.845.0 VNNSCULKATENGCUNKTAKTESACURPSKAATEGACURPSKAAT	GO:0043065	positive regulation of apoptotic process	12/101	1.77E-07	8.55E-06	SRC/TNF/ABL1/HMGB1/MMP2/PDGFRB/TOP2A/RPS6KA2/RARB/DNM2/NCOA1/RBCK1
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GO:0007173epidermal growth factor receptor signaling pathway3/1012.78E-031.60E-02SRC/ABL1/PTK2GO:0042789mRNA transcription by RNA polymerase II3/1012.78E-031.60E-02RARA/NCOA1/HLTF	GO:0051239	regulation of multicellular organismal process	2/101	2.54E-03	1.51E-02	TNF/PTK2
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GO:0043124 negative regulation of I-kappaB kinase/NF-kappaB signaling 3/101 2.78E-03 1.60E-02 ABL1/RHOA/RHOH						
	GO:0043124	negative regulation of I-kappaB kinase/NF-kappaB signaling	3/101	2.78E-03	1.60E-02	ABL1/RHOA/RHOH

GO:0030324	lung development	4/101	2.82E-03	1.61E-02	KDR/VEGFA/FGF2/FGFR2
GO:0060644	mammary gland epithelial cell differentiation	2/101	2.95E-03	1.64E-02	FGF2/SMO
GO:0010718	positive regulation of epithelial to mesenchymal transition	3/101	2.95E-03	1.64E-02	PTK2/IL1B/HDAC2
GO:0031648	protein destabilization	3/101	3.12E-03	1.71E-02	SRC/PLK1/MDM2
GO:0006351	DNA-templated transcription	7/101	3.15E-03	1.71E-02	RARA/NR3C1/DNMT1/RARB/PPP5C/KAT6A/KDM2A
GO:0071168	protein localization to chromatin	2/101	3.39E-03	1.77E-02	PLK1/MCM8
GO:0048146	positive regulation of fibroblast proliferation	3/101	3.49E-03	1.81E-02	ABL1/PDGFRB/CDK6
GO:0050727	regulation of inflammatory response	4/101	3.60E-03	1.86E-02	LYN/TNF/TLR4/HCK
GO:0090398	cellular senescence	3/101	3.89E-03	1.94E-02	ABL1/MAPKAPK5/KAT6A
GO:000086	G2/M transition of mitotic cell cycle	3/101	4.10E-03	2.02E-02	AURKA/PLK1/DNM2
GO:0034097	response to cytokine	3/101	4.31E-03	2.08E-02	MMP2/RARA/MAPKAPK3
GO:0071456	cellular response to hypoxia	4/101	4.80E-03	2.21E-02	SRC/VEGFA/DNMT3A/MDM2
GO:0030889	negative regulation of B cell proliferation	2/101	4.88E-03	2.21E-02	LYN/BLK
GO:0036211	protein modification process	4/101	5.10E-03	2.30E-02	ABL1/CDC34/UBE2M/UBE2L6
GO:0033189	response to vitamin A	2/101	5.44E-03	2.38E-02	RARA/DNMT3A
GO:2000811	negative regulation of anoikis	2/101	5.44E-03	2.38E-02	SRC/PTK2
GO:0010468	regulation of gene expression	7/101	5.54E-03	2.39E-02	CDK6/DNMT3A/MDM2/SMO/DNMT1/SMARCA4/DNMT3B
GO:0070301	cellular response to hydrogen peroxide	3/101	5.99E-03	2.53E-02	SRC/ABL1/HDAC2
GO:0043154	negative regulation of cysteine-type endopeptidase activity involved in ap	c 3/101	6.54E-03	2.73E-02	SRC/TNF/VEGFA
GO:0002223	stimulatory C-type lectin receptor signaling pathway	2/101	6.63E-03	2.74E-02	LYN/SRC
GO:000082	G1/S transition of mitotic cell cycle	3/101	6.82E-03	2.81E-02	CDK6/POLE/CDC34
GO:0001932	regulation of protein phosphorylation	3/101	7.71E-03	3.16E-02	LYN/TNF/PTK2
GO:0060045	positive regulation of cardiac muscle cell proliferation	2/101	7.92E-03	3.21E-02	FGF2/FGFR2
GO:0032091	negative regulation of protein binding	3/101	1.00E-02	3.85E-02	AURKA/KDM1A/AURKB
GO:0048714	positive regulation of oligodendrocyte differentiation	2/101	1.01E-02	3.85E-02	HDAC2/CXCR4
GO:0008285	negative regulation of cell population proliferation	7/101	1.09E-02	4.11E-02	LYN/TNF/IL1B/FGF2/RARA/CDK6/RPS6KA2
GO:0032148	activation of protein kinase B activity	2/101	1.24E-02	4.43E-02	SRC/ADRA2C
GO:0035924	cellular response to vascular endothelial growth factor stimulus	2/101	1.24E-02	4.43E-02	KDR/VEGFA
GO:0043200	response to amino acid	2/101	1.24E-02	4.43E-02	LYN/RHOA
GO:0071480	cellular response to gamma radiation	2/101	1.24E-02	4.43E-02	KDM1A/MDM2
GO:0010592	positive regulation of lamellipodium assembly	2/101	1.33E-02	4.70E-02	RAC1/DNM2
GO:0097421	liver regeneration	2/101	1.41E-02	4.88E-02	TNF/AURKA

Table S9. Description for scores and filters on PandaOmics.

Category	Score/ Filter	Description
Omics AI scores	Network Neighbors	This score utilizes several graph-based methods applied to the protein-protein interaction network enriched with differentially expressed/methylated genes. The score explores direct network neighbors interacting with a given gene. A target will be scored higher if there are more network neighbors with significant differences in expression or methylation levels.
	Casual Inference	This score is based on the causal inference of transcription factors. It estimates the number of genes associated with the disease progression/treatment, controlled by a similar set of transcription factors to a given gene. It uses a manually curated regulatory network and known drug targets to predict potential disease-modifying transcription factors.
	Pathways	The score combines several approaches to pathway analysis. First, iPANDA algorithm is used to examine the involvement of a given gene in pathway activation patterns based on a collection of gene expression datasets of interest (activation/inhibition of each pathway is examined separately). Next, all the pathways from the library are merged into a single network, which is examined from the perspective of signal propagation by a number of methods. The final score indicates how a given gene affects individual pathways' activation/inhibition, and whether it possesses the ability to affect multiple pathways at once.
	Interactome Community	This score utilizes several graph-based methods applied to the protein-protein interaction network enriched with active drug targets, GWAS hits and differentially expressed/methylated genes.
	Relevance	This score is based on open data from the OpenTargets resource, in particular, Drugs score. Drugs score aggregates general information about all drugs and their stages of clinical trials that are associated with a specific gene (protein, molecular target) for a disease of interest. The more drugs that have a specific gene as a molecular target, especially in the late phases of clinical trials, the higher the Drugs score for that gene.
	Expression	This score takes into account differential gene expression, protein abundance or methylation level defined by a collection of datasets of interest. Machine learning-based models are used to normalize available omics data across multiple samples from various datasets.

	Heterogeneous Graph Walk	This score is a guided random walk-based approach that is applied to a heterogeneous graph (i.e., a graph containing different types of nodes). The model learns node representations and then finds the gene nodes similar to the reference disease node. First, the "walks" are sampled with a predefined meta-path, i.e., the fixed sequence of node types in a walk, e.g. 'gene'-'disease'-'gene.' The node degree controls the probability of transition between the nodes while sampling. Following that, the AI model learns the representation of each node based on the resulting corpus of walks. The similarity between the specific disease and all available genes produces a ranked list of genes. The top genes from this list are predicted to be promising target hypotheses.
	Matrix Factorization	This score is based on a collaborative filtering algorithm, which is widely used in recommender systems. First, well-known gene-disease associations from the PandaOmics database are converted to a sparse binary matrix. This matrix is then decomposed into two low-rank matrices that consist of latent factors for genes and diseases. The algorithm uses graph regularization based on a fast kNN search to account for the intraclass similarity between the nodes of a similar type. Recomputing the original interaction matrix from latent factors provides the scores for unobserved interactions; thus, gene ranking is obtained.
Text-based AI scores	Evidence	This score is calculated as the weighted average of Trend and Attention score. Higher values indicate both attention growth and a high volume of research.
	Attention Score	This score measures the overall attention to the target at all times. PandaOmics calculates the total number of mentions of a gene in various texts across all time periods. Both disease-agnostic and disease-specific mentions are counted. Text corpus used for analysis includes scientific publications, grants, patents and clinical trials.
Financial Scores	Grant Funding	Total grant funding to investigate the given gene at all times. Please note, that the distribution of total funding is skewed with mean value approx. \$8.9 million, but the median value is only \$1.7 million. Also 5% of entries have funding above \$30 million.
KOL Scores	Credible Attention Index Impact factor	This score represents the total number of publications devoted to the target gene in journals with an impact factor more than 10. This corresponds to the top 3% of all scientific journals. This score measures the average impact factor of the journals where particular gene-disease association is published. The Impact Factor of each journal is weighted to the number of publications mentioning gene-disease association published in this journal.

Druggability Filter	Small Molecules	Indicates accessibility of a protein by small molecules
		Red - A protein does not belong to a druggable class and does not have small molecules associated Yellow - A protein belongs to a druggable class and does not have small molecules associated Green - A protein is associated with small molecules according to public sources and the PandaOmics manually curated database
	Antibodies	Indicates the ability to use antibodies to hit the target
		Red - It is not membrane secreted protein (Protein atlas database) Yellow - A membrane secreted protein (Protein atlas database) Green - A membrane secreted protein (Protein atlas database) with associated antibodies in TCRD database
	Safety	Potential safety of a target and potential adverse effect
		Red - A protein is an essential gene and did not pass any clinical trials (Clinical trials and TTD) Yellow - Default status Green - A protein is a conditional essential gene or is not essential and has clinical trials going on or passed (Clinical trials and TTD)
	Novelty	Indicates the overall scientific community interest to the target, based on the volume of related publications proposed by the proprietary AI engine
		Red - More than 168 publications on pharmacognitive Yellow - Between 50 and 168 publications on pharmacognitive Green - Less than 49 publications on pharmacognitive
Target Familes	Enzyme Epigenetic enzyme Epigenetic nonenzyme Generic protein Ion channel Kinase Nuclear receptor Receptor Secretory protein	Druggable Druggable Not druggable Druggable Druggable Druggable Druggable Druggable

Transcription coregulator	Not druggable
Transcription factor	Not druggable
Transportor	Druggable