



Cellular Senescence and Resilience: Potential Roles of Senolytics, Checkpoint Inhibitors, and Senosensitizers

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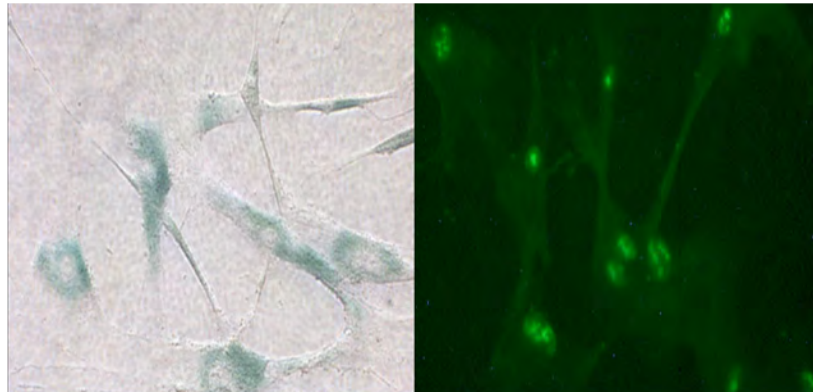
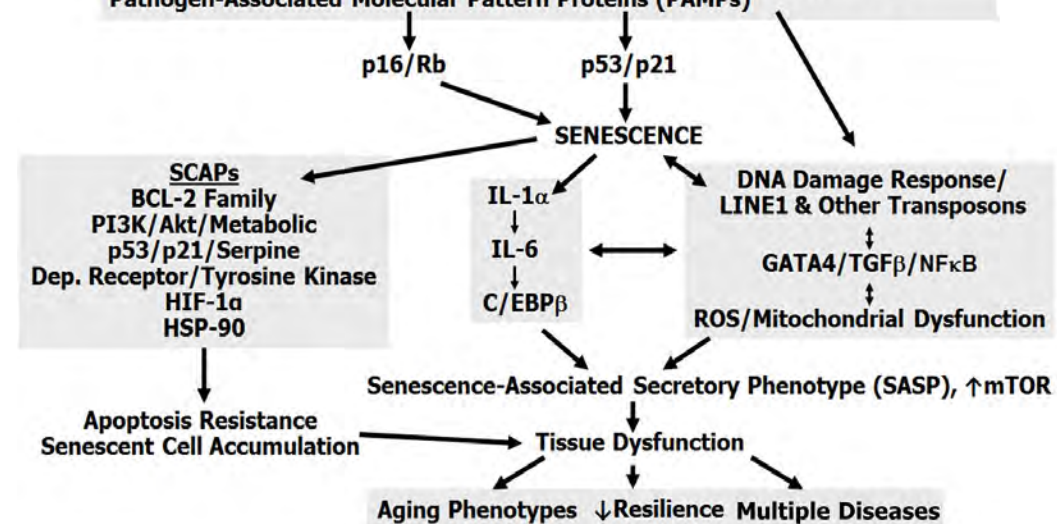
**AGS/NIA R13 Bench-to-Bedside Conference Series
Optimizing Resilience**

Bethesda

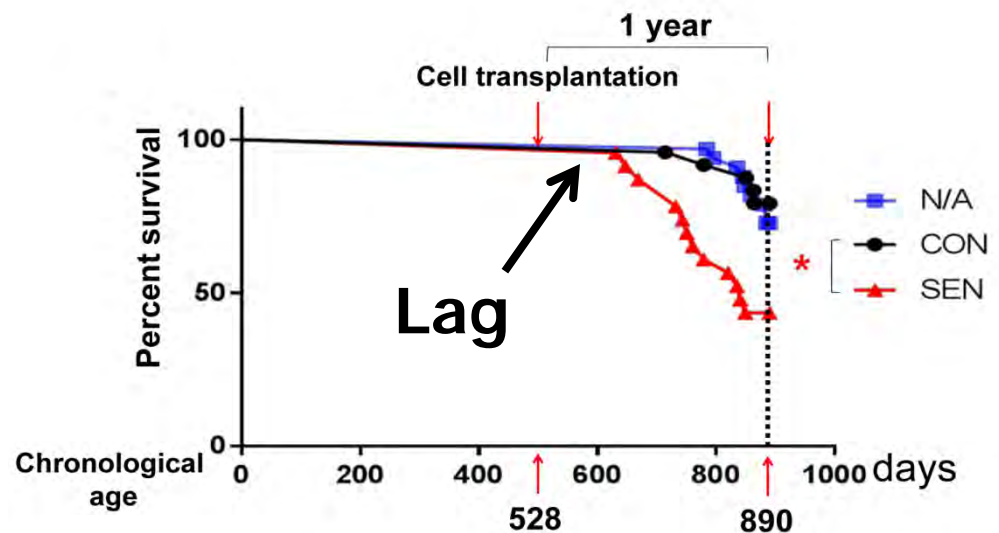
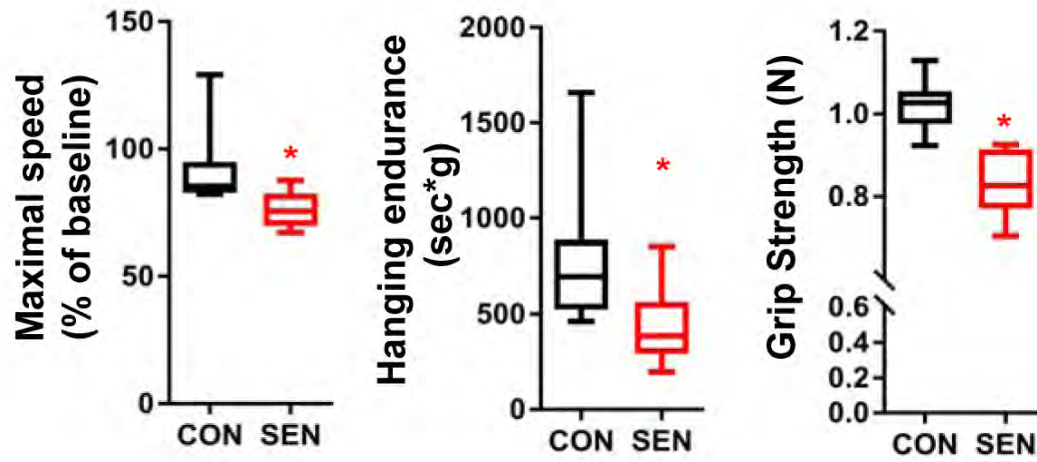
March 3, 2026

Cellular Senescence: A Cell Fate

DNA Damage (telomere shortening, mutations, alkylating agents, radiation)
 Oncogenes (*e.g.*, Ras, Myc)
 Reactive Metabolites (ROS, ceramides, fatty acids, leukotrienes, high glucose)
 Mitogens/ IGF-1
 Proteotoxic Stress (protein aggregation, unfolded protein response, mTOR)
 Mechanical Stress, Shear Stress, Hypoxic or Hyperoxic Stress
 Inflammation, Damage-Associated Molecular Pattern Proteins (DAMPs),
 Pathogen-Associated Molecular Pattern Proteins (PAMPs)



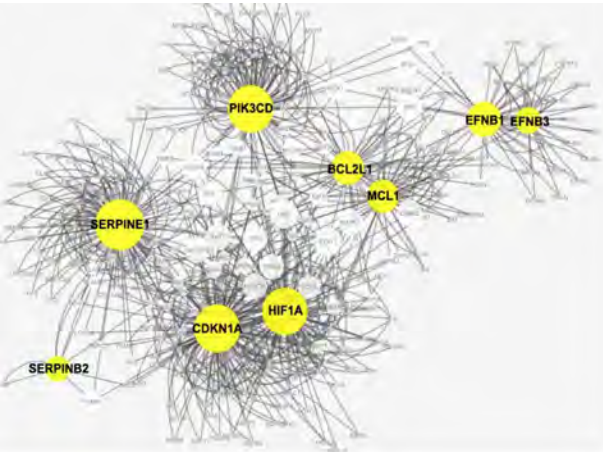
Transplanting Senescent Cells Causes Physical Dysfunction and Decreases Survival



Senescence induced by 10 Gy radiation

Xu *et al.*,
Nature
Medicine,
2018

Senolytics



1st Generation Mechanism-Based

Discovered by Identifying SCAPs and Then Selecting Drugs with Known SCAP Targets

Dasatinib
Quercetin
Fisetin
Luteolin
Enzastaurin
Navitoclax (ABT263)
A1331852
A1155463
Piperlongumine
Cardiac Glycosides
Chloroquine

Geldanamycin
Tanespimycin
Alvespimycin
Procyanidin C1
Birinapant
LCL161
Warburg shift

More being developed

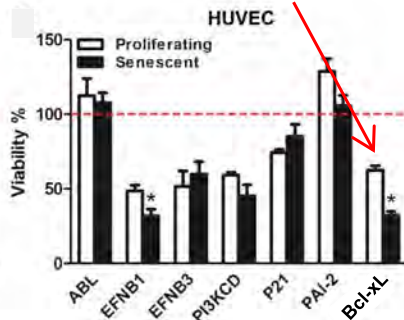
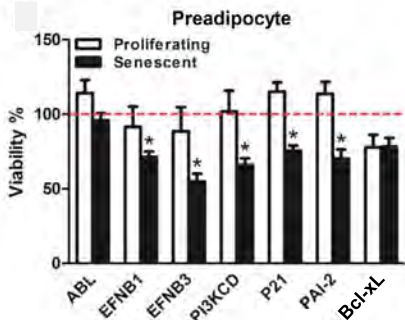
2nd Generation Randomly Identified

Identified by Chance or with High-Throughput Compound Library Screens

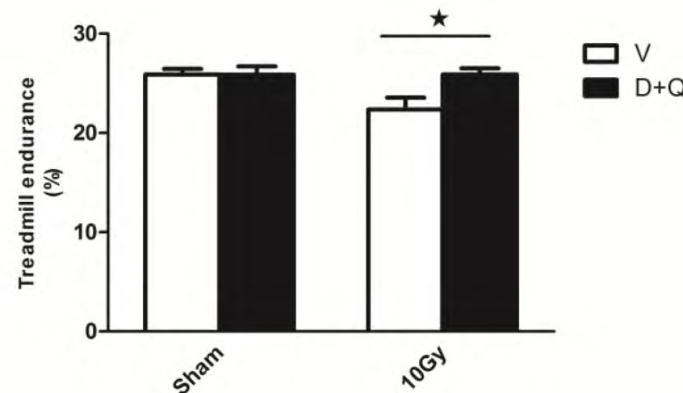
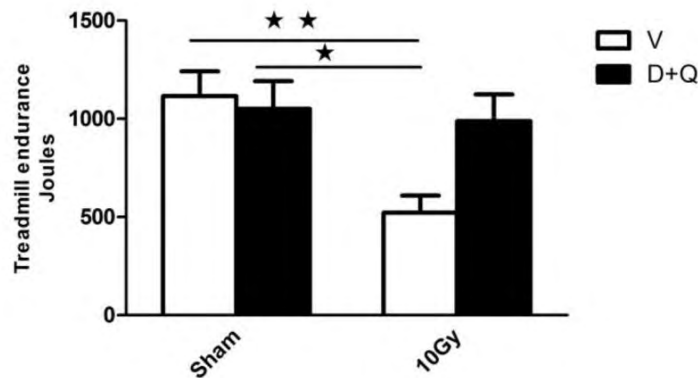
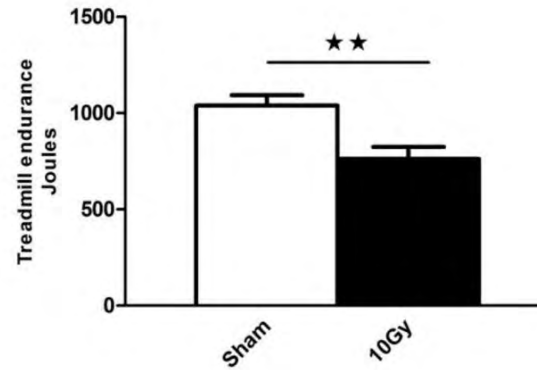
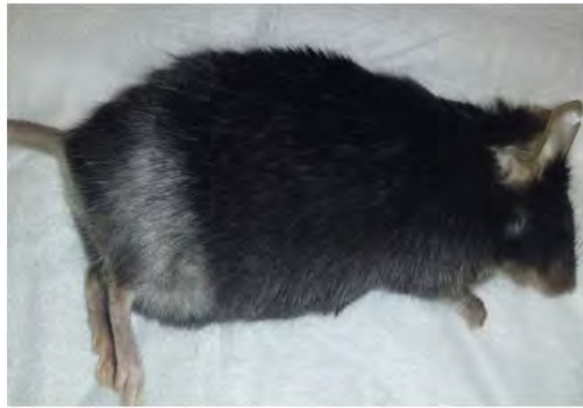
Zoledronate
SGLT-2 Inhibitors
More being developed

Other approaches:

Immunomodulators
CAR-T
Vaccines
SA β -gal-activated toxins
miRNAs
Nanoparticle Toxins
Trilocked PDSI's
Mechanical Susceptibility
Electrical Fields
Others



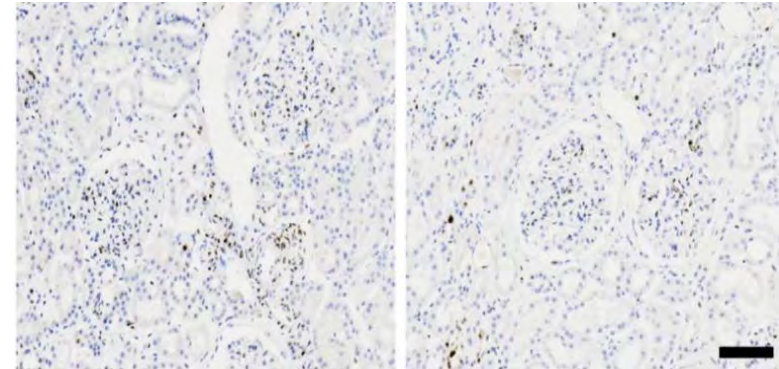
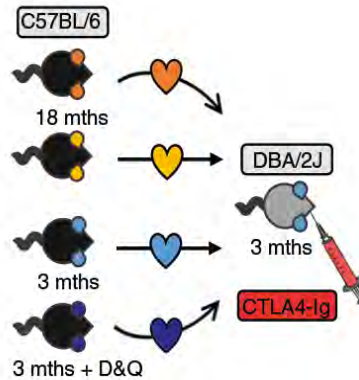
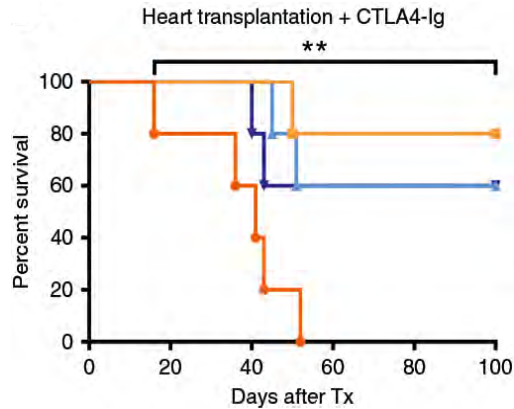
A Single Dose of Senolytics Alleviates Radiation-Induced Gait Disturbance for at Least 7 Months



N=6-9 mice/
group;
* $P < 0.05$;
** $P < 0.001$

Zhu *et al.*,
Aging Cell
March, 2015

Organ Transplantation



Six discarded human kidneys were treated with senolytics (1 μ M D & 20 μ M Q) for 24 hrs. Biopsy samples were collected pre- and post-treatment. D+Q reduced p21^{CIPI}+ cells by 30% (two-tailed Mann-Whitney $p < 0.05$).

Unpublished

C57BL/6 mice were treated with D+Q or PBS prior to fully mismatched cardiac transplantation. Recipients were treated weekly with CTLA4-IG, a fusion protein of CLTA-4 and IgG that blocks the interaction of CD80/86 with CD28 on naive T cells. Allograft survival was monitored by daily palpation. N=at least 3 independent expts.



Nat Commun. 2020 Aug 27. PMID: 32855397;
Am J Transplant. 2023 Oct 30. PMID: 37913871

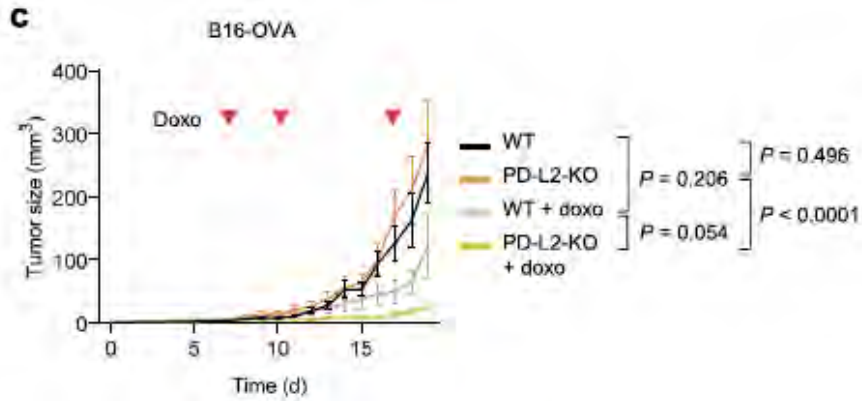
Emerging Evidence for Benefits of Senolytics For:

Diabetes/ Obesity
Age-Related Lipodystrophy
Cardiac Dysfunction
Vascular Hyporeactivity/ Calcification/ AV Fistulae
Frailty/ Sarcopenia
Response to Chemotherapy/ Response to Radiation
Sequelae of High-Altitude Flight and Space Travel
Cancer
Sequelae of Bone Marrow Transplantation
Sequelae of Organ Transplantation
Myeloma/ MGUS
Cognition/ Alzheimer's/ Parkinson's/ ALS/ Anxiety/ Down syndrome/
Temporal Lobe Epilepsy
Renal Dysfunction
Osteoporosis/ Osteoarthritis/ Rheumatoid Arthritis/ Degenerated Discs
COPD/ Idiopathic Pulmonary Fibrosis/ Tobacco/ Hyperoxic Lung Damage
Hepatic Steatosis/ Liver Cirrhosis/ Primary Biliary Cirrhosis
Progerias
Critical Illness Myopathy
Pre-eclampsia/ Uterine Fibrosis/ Ovarian Involution
Cataracts/ Macular Degeneration/ Glaucoma
Prostatic Hypertrophy
Skin Disorders
Stem Cell Activation/ Progenitor Dysfunction
COVID-19
Gingivitis/ Periodontal Disease

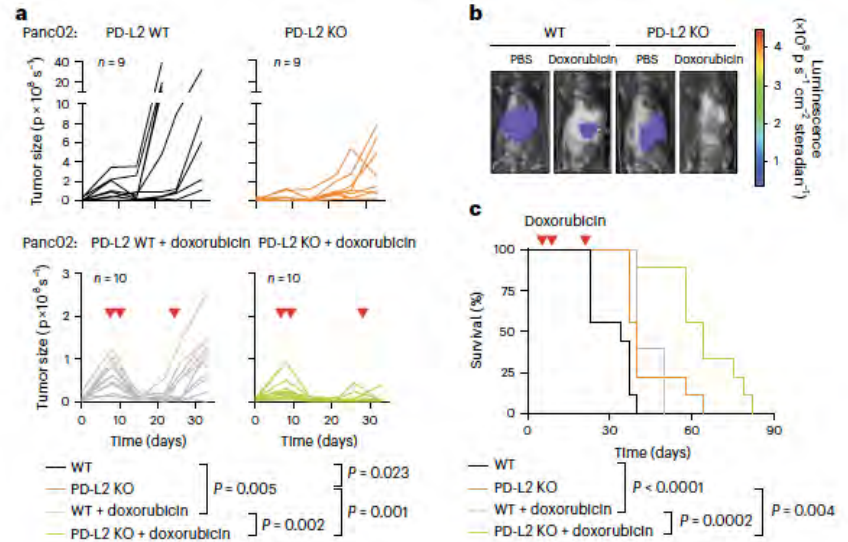


Targeting PD-L2 in various cancer models improves therapeutic outcome

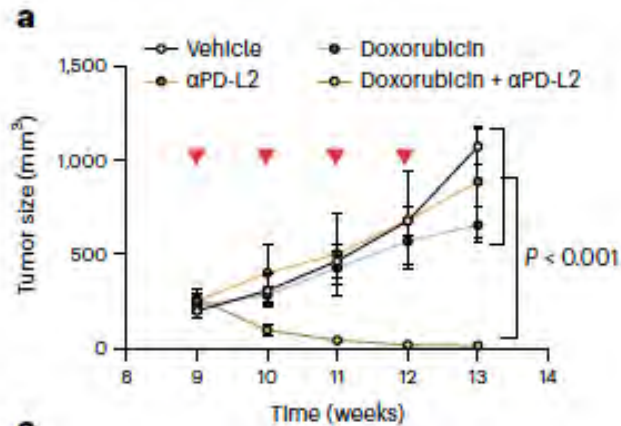
Melanoma

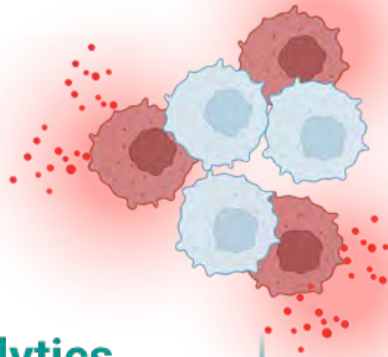
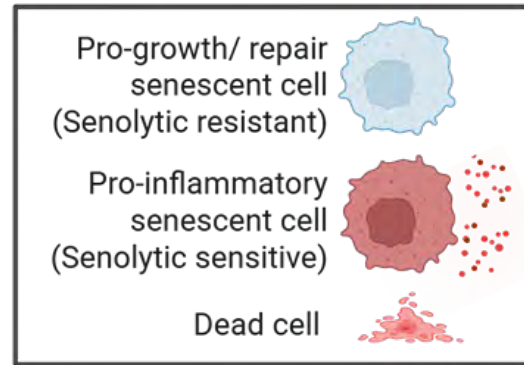


Pancreatic cancer



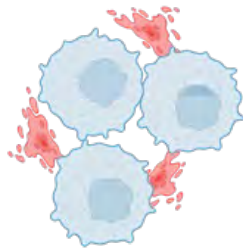
Breast cancer





Senolytics

Killing of pro-inflammatory senescent cells



Time, infection, other chronic conditions,
Senosensitizer

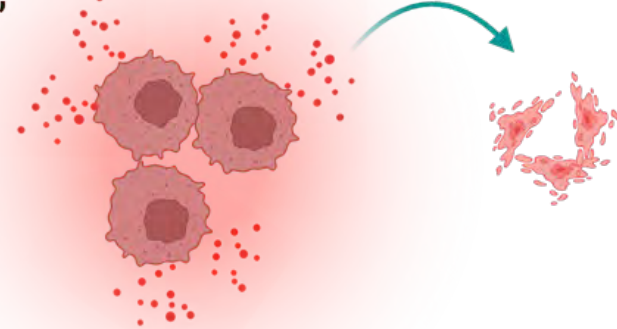


Senomorphics



Senolytics

Killing of pro-inflammatory senescent cells



SC subset expressing high growth factor / fibrotic SASP
Wound healing, growth, and remodeling



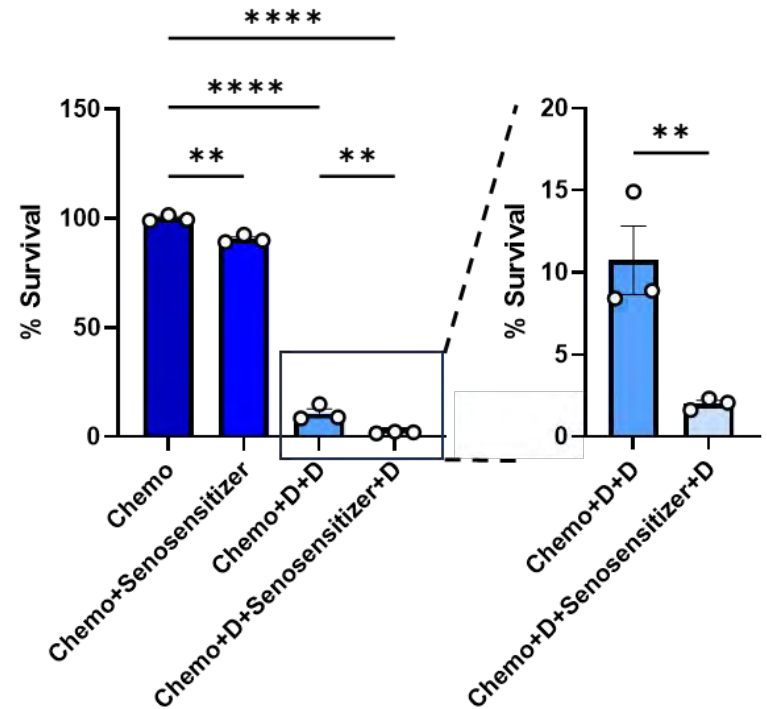
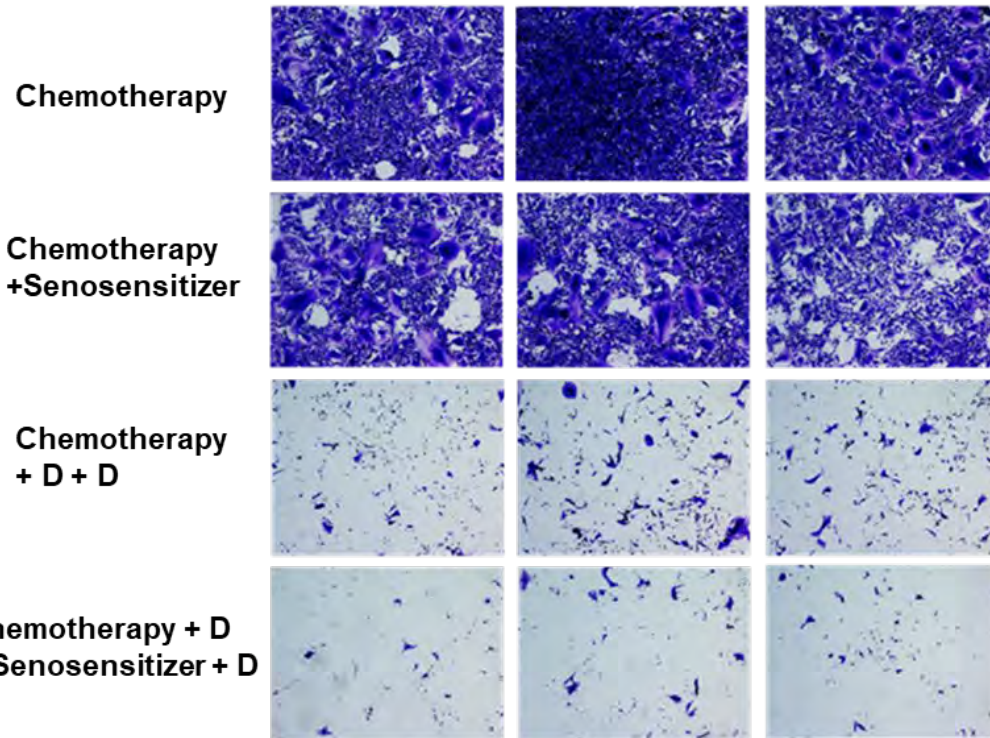
- Improved tissue function
- Decrease of age-related diseases
- Improve resilience
- Pro-cancerous microenvironment

SC subset expressing high pro-inflammatory, pro-apoptotic SASP

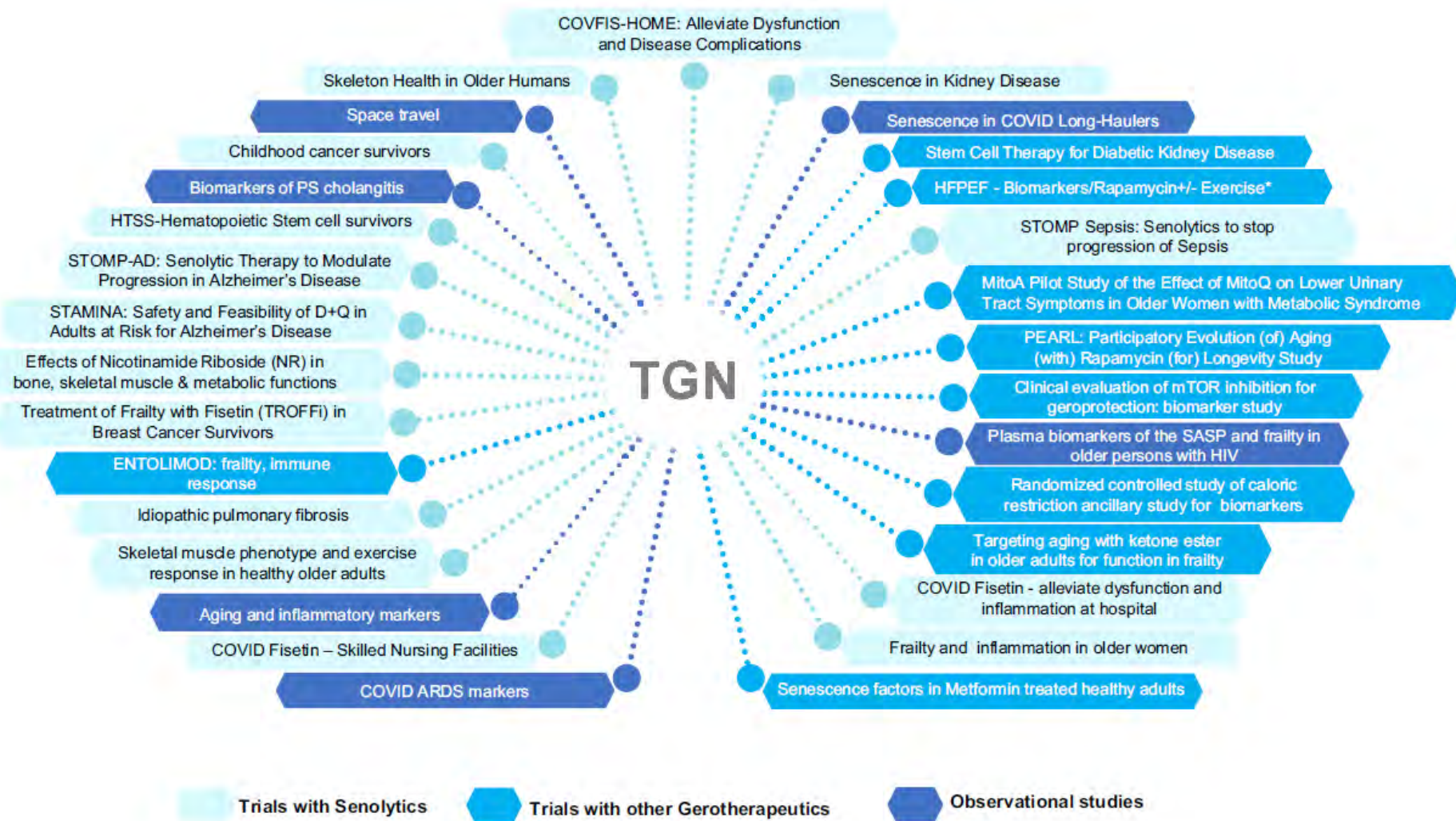
Senosensitizers Induce Senolytic-Resistant SCs to be Converted into SCs That are Susceptible to Senolytics

A "1:2:3:4"-Step Approach Enhances Ablation of Cultured Triple-Negative Breast Cancer Cells

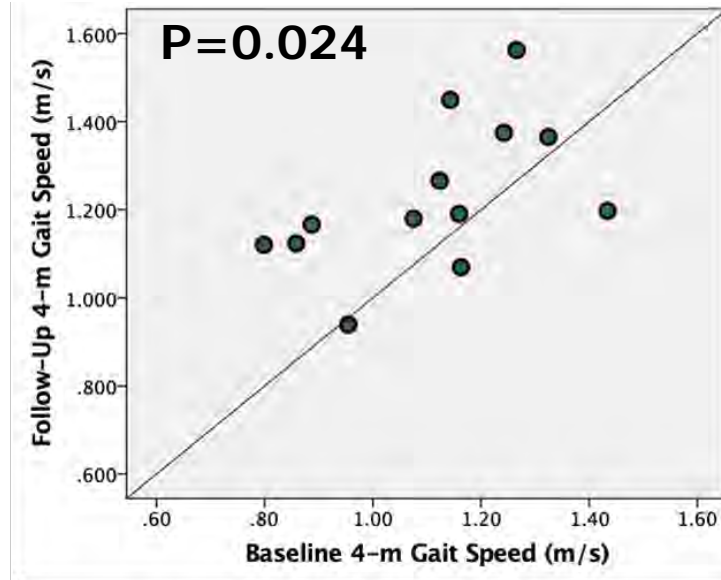
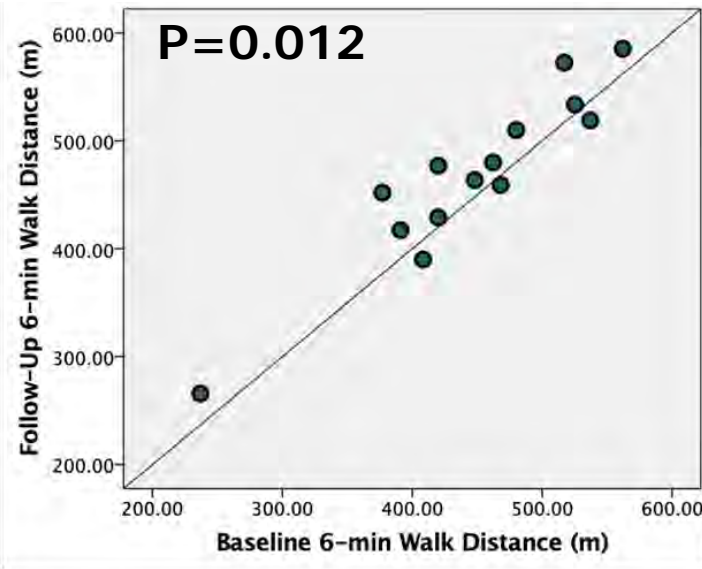
Senosensitizer: TLR3 agonist (polyinosinic-polycytidylic acid)



Selected Examples of TGN Affiliated Clinical Trials (120 Completed, Underway, About to Begin, or Planned)



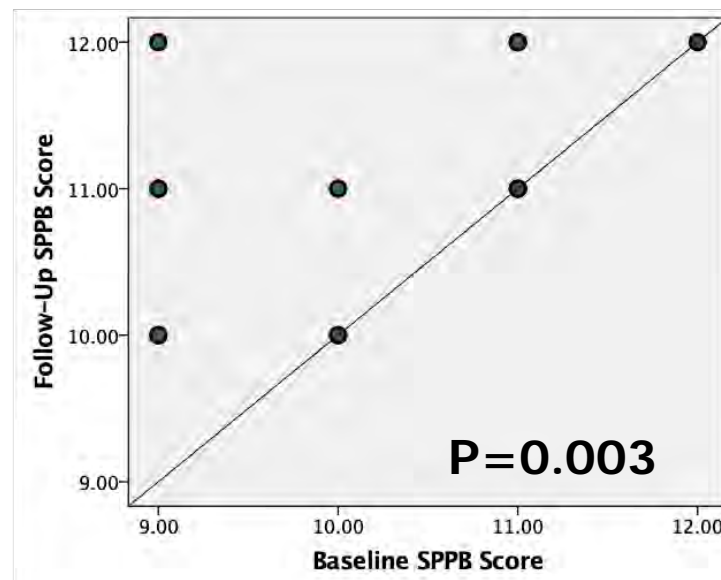
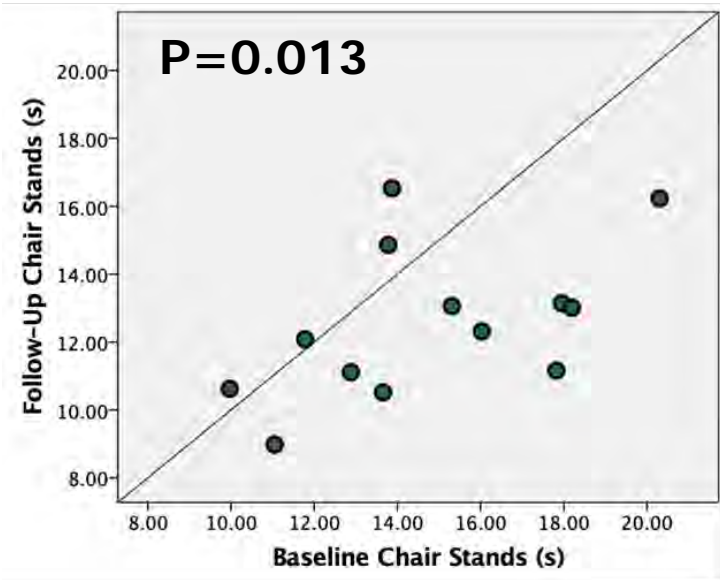
First-in-Human Trial of Senolytics: D+Q for Idiopathic Pulmonary Fibrosis



No severe
adverse
events

9 doses/ 3
wks

Functional
measures 5
days after
last dose





MCI/ Stage 1 Alzheimers

EBioMedicine. 2025 Mar:113:105612. doi:
10.1016/j.ebiom.2025.105612

100 mg D, 1250 mg Q for 2 days/ 2 weeks/ 12 weeks

N = 12

Mean Montreal Cognitive Assessment (MoCA) scores non-significantly increased following DQ by 1.0 point (95% CI: -0.7, 2.7), but increased significantly by 2.0 points (95% CI: 0.1, 4.0) in those with lowest baseline MoCA scores

TNF- α changes were significantly and inversely correlated with MoCA changes ($r=-0.65$, $p=0.02$), such that reductions in TNF- α were correlated with increases in MoCA

Protein/Peptide Analytes in Circulation (Plasma/Serum)

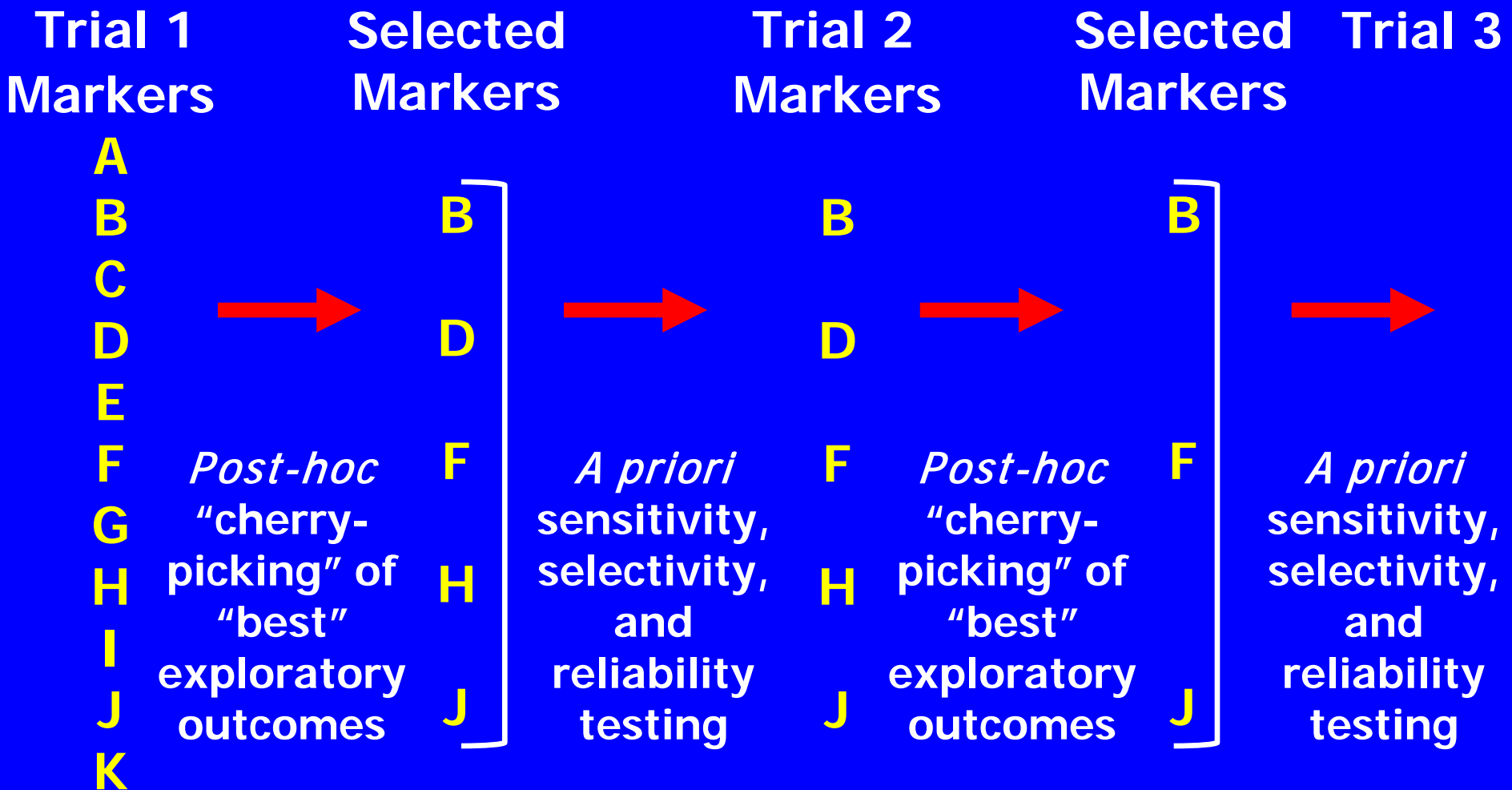
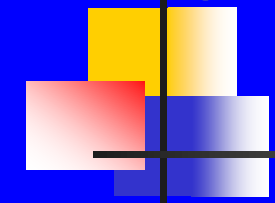
#	Analyte	Standard Curve (pg/mL)
1	ADAMTS13	16000 - 3900000
2	Adiponectin/Acrp30	823 - 200000
3	CCL11/Eotaxin	31.6 - 23,000
4	CCL17/TARC	103 - 25000
5	CCL18/PARC	18.5 - 4500
6	CCL19/MIP-3 beta	3.9 - 2,850
7	CCL2/IE/MCP-1	4.5 - 3,300
8	CCL20/MIP-3 alpha	2.2 - 1,600
9	CCL22/MDC	53.5 - 13000
10	CCL5/RANTES	20.6 - 5000
11	CRP	32.8-50000
12	CX3CL1/Fractalkine	617 - 150000
13	CXCL1/GRO alpha/KC/CINC-1	57.6 - 14,000
14	CXCL10/IP-10/CRG-2	2.5 - 1,800
15	CXCL2/GRO beta/MIP-2/CINC-3	9.8 - 7,000
16	Cystatin C	580 - 140000
17	EGF	6.7 - 4,880
18	Fas/TNFRSF6/CD95	144 - 35000
19	Flt-3 Ligand/FLT3L	21.9 - 16,000
20	GDF-15	18.5 - 4500
21	HGF	16.5 - 4000

#	Analyte	Standard Curve (pg/mL)
22	Human Activin A	15.6-1000
23	Human IGF-I	100-4000
24	ICAM-1/CD54	7000 - 1700000
25	IFNg	0.17-4000
26	IGFBP-2	712 - 175000
27	IGFBP-3	1650 - 400000
28	IL-10	0.58-2212
29	IL-18	0.96-3660
30	IL-1ra/IL-1F3	11 - 8,000
31	IL-6	0.28-6630
32	IL-7	3.65-5570
33	IL-8	0.19-1804
34	M-CSF	103 - 25000
35	MIF	556 - 135000
36	MMP-1	49.4 - 12000
37	MMP-10	53.7 - 13000
38	MMP-2	276 - 67000
39	MMP-3	82.3 - 20000
40	MMP-7	226 - 55000
41	MMP-8	226 - 55000
42	MMP-9	123 - 30000

#	Analyte	Standard Curve (pg/mL)
43	Myeloperoxidase/MPO	123 - 30000
44	Osteoactivin/GPNMB	45-12000
45	Osteopontin/OPN	1440 - 350000
46	PDGF-AA	6.6 - 4,800
47	PDGF-AB/BB	6.9 - 5,000
48	PD-L1/B7-H1	5.9 - 4,320
49	PD-L2	46.2-33670
50	RAGE/AGER	123 - 30000
51	Serpin E1/PAI-1	18.1 - 4400
52	SOST/Sclerostin	10.3 - 2500
53	Stanniocalcin 1/STC-1	123 - 30000
54	TGFb1	20.8-12684
55	TNF RI/TNFRSF1A	49.4 - 12000
56	TNF RII/TNFRSF1B	11.1 - 2700
57	TNF-a	0.3-2900
58	TRAIL/TNFSF10	24 - 17,500
59	uPAR	1.68-16000
60	VCAM-1/CD106	8850 - 2150000
61	VEGF	6.4 - 4,700

Also ROS & NAD indicators, bioactive small molecules (e.g., prostanoids), & non-coding nucleotides (e.g., miRNAs, mtDNA)

Iterative Channeling Strategy to Develop a Clinically-Relevant Gerodiagnostic Composite Biomarker Score





TGN Clinical Trials of Gerotherapeutics to Enhance Resilience

Underway or About to Begin:

- Organ and systemic function in recipients of kidneys, hearts, livers, whole pancreases, or skin transplants from older donors treated *ex vivo* with senolytics
- Pretreating older subjects with senolytics *vs.* vehicle to prevent or attenuate delirium following elective hip surgery
- Severity of influenza in subjects with increased senescent cell burden treated with senolytics *vs.* vehicle shortly before infection
- Topical or systemic senolytics *vs.* vehicle for skin wound repair in older subjects before/shortly after elective surgery

Being Planned (Among Others):

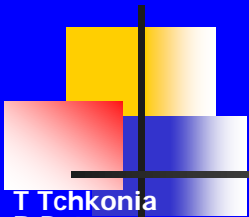
- Senolytic pretreatment to allow higher doses and attenuate adverse effects of radiation/chemotherapy for cancers beginning with radiation for esophageal cancer



Conclusions

- Persistent senescent cells cause inflammation, fibrosis, progenitor cell dysfunction, spread of senescence, and multiple disease- and age-related disorders
- The target of senolytics, particular checkpoint inhibitors, and senosensitizers followed by senolytics is senescent cells, not a single molecule or pathway
- These interventions can attenuate tissue inflammation and fibrosis, improve function, reduce rejection after transplanting organs from old individuals, and target cancer-harboring senescent cells and TIS
- “Hit and run” intermittent treatment may be effective for enhancing resilience and delaying or alleviating multiple diseases, improving tissue regeneration, and enhancing healthspan in mice
- These agents could lead to interventions for humans that delay, prevent, alleviate, or treat senescence- and age-related conditions if clinical trials continue to demonstrate effectiveness and low toxicity

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