

T cell ageing and its impact on alloimmunity

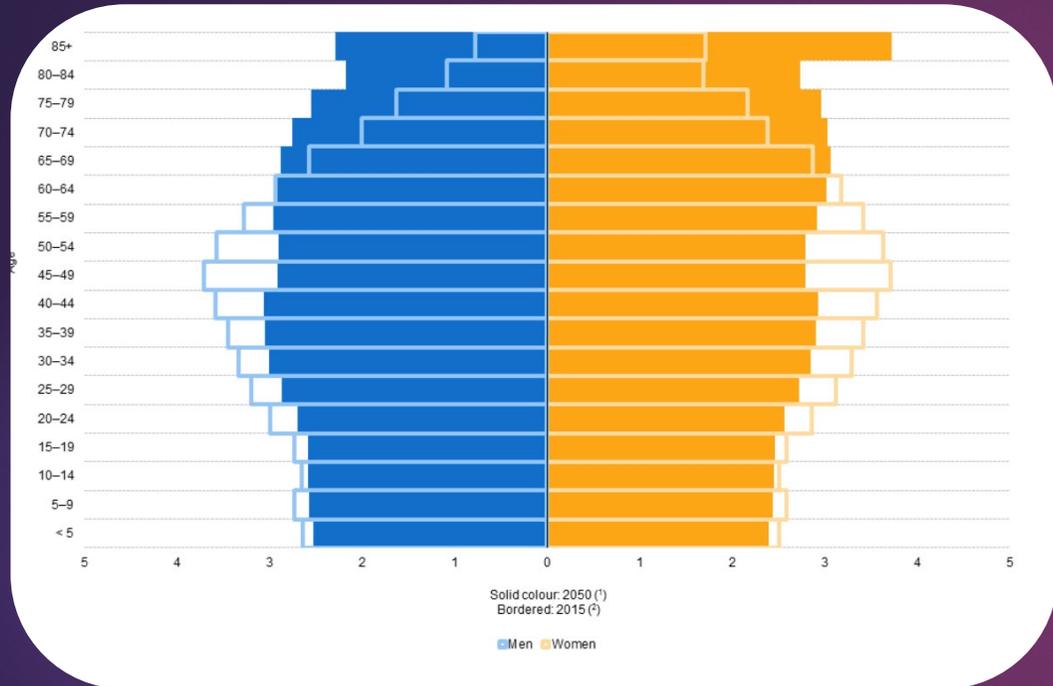
Jasper Iske

Deutsches Herzzentrum der Charité



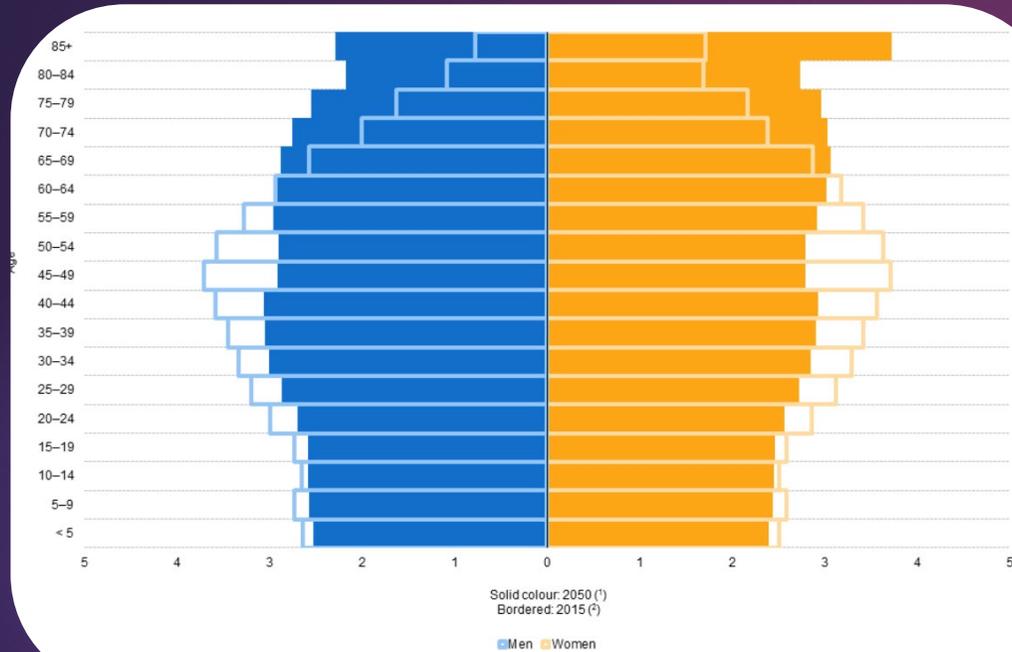
Background

Demographics Europe 2050



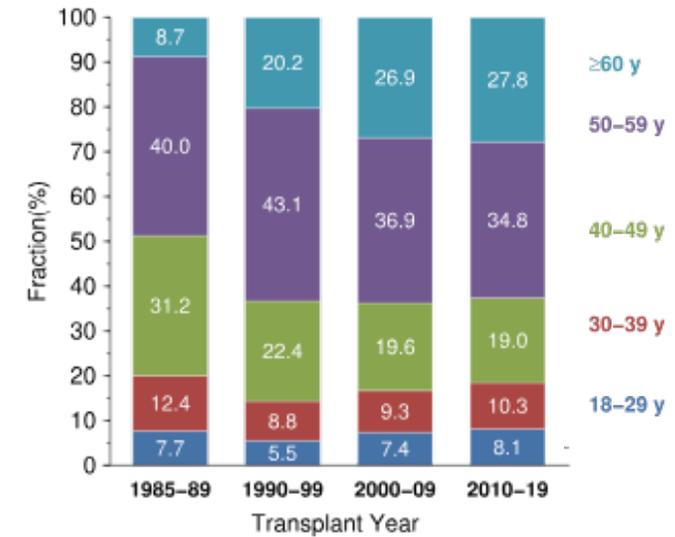
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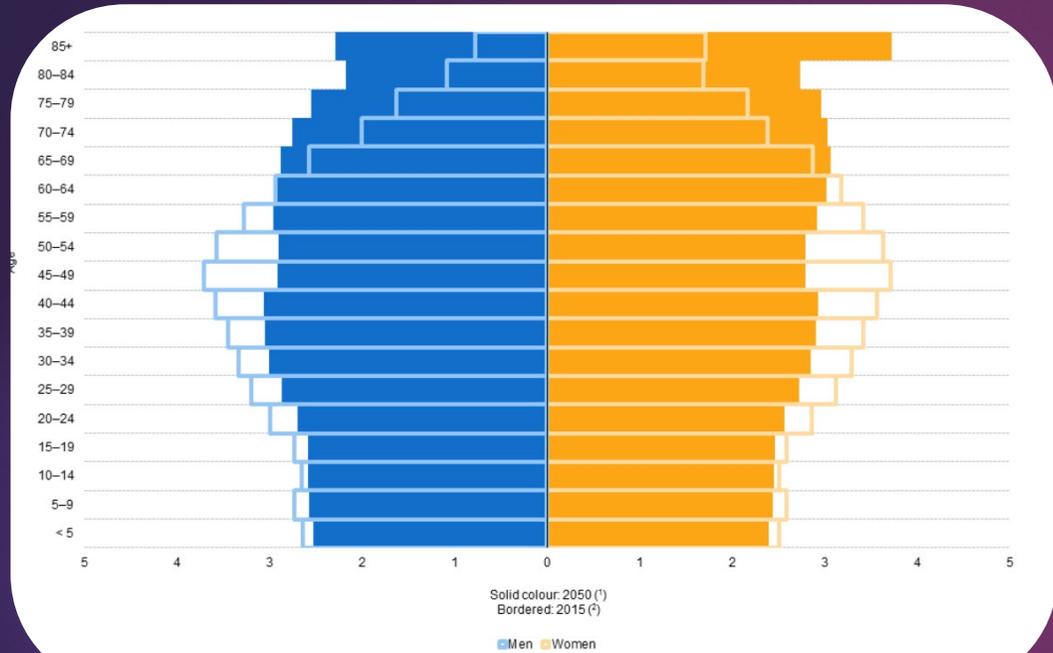
Recipient Demographics

(A) Recipient Age

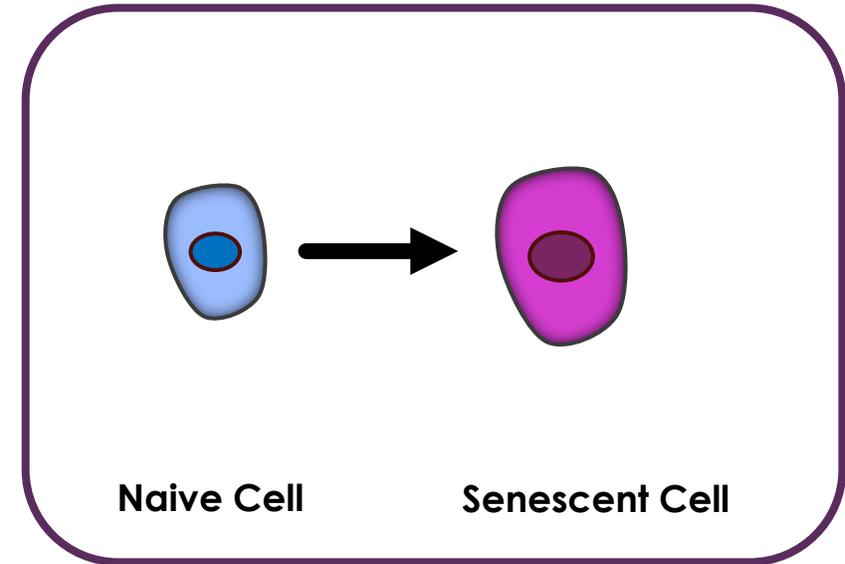


Background

Demographics Europe 2050

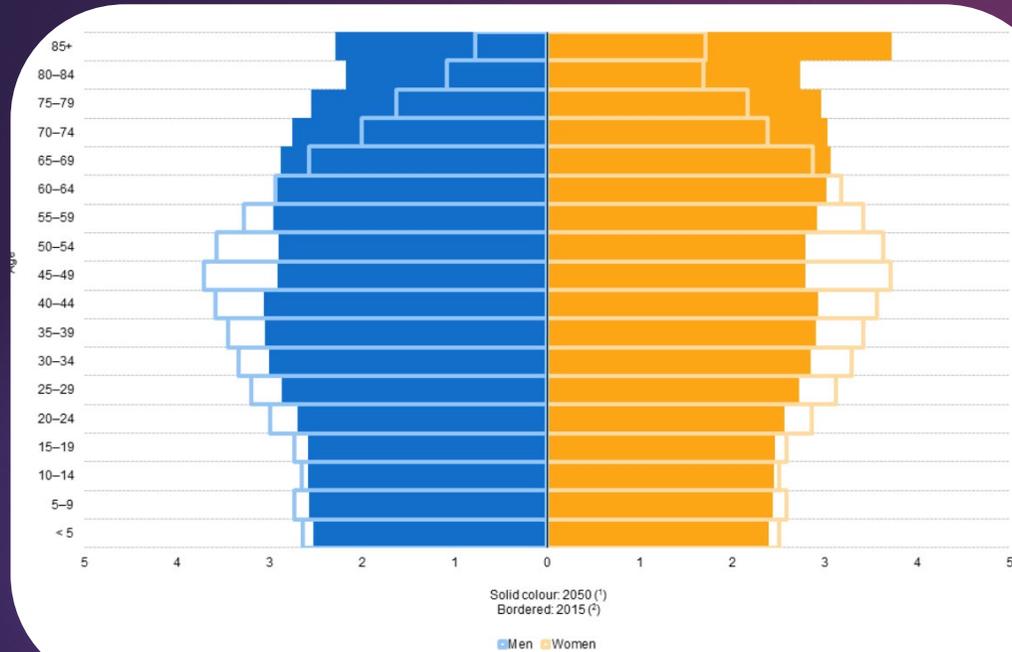


Senescence

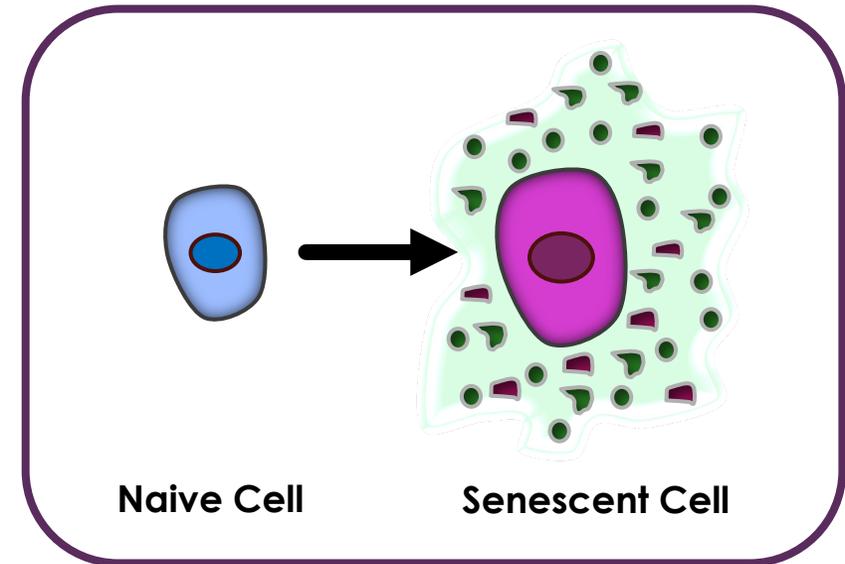


Background

Demographics Europe 2050

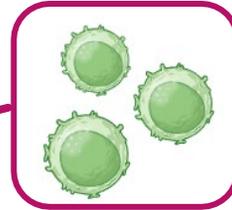


Senescence



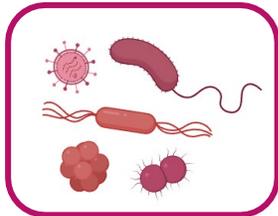
Major Obstacles during Transplantation in the Elderly

Immunosenescence

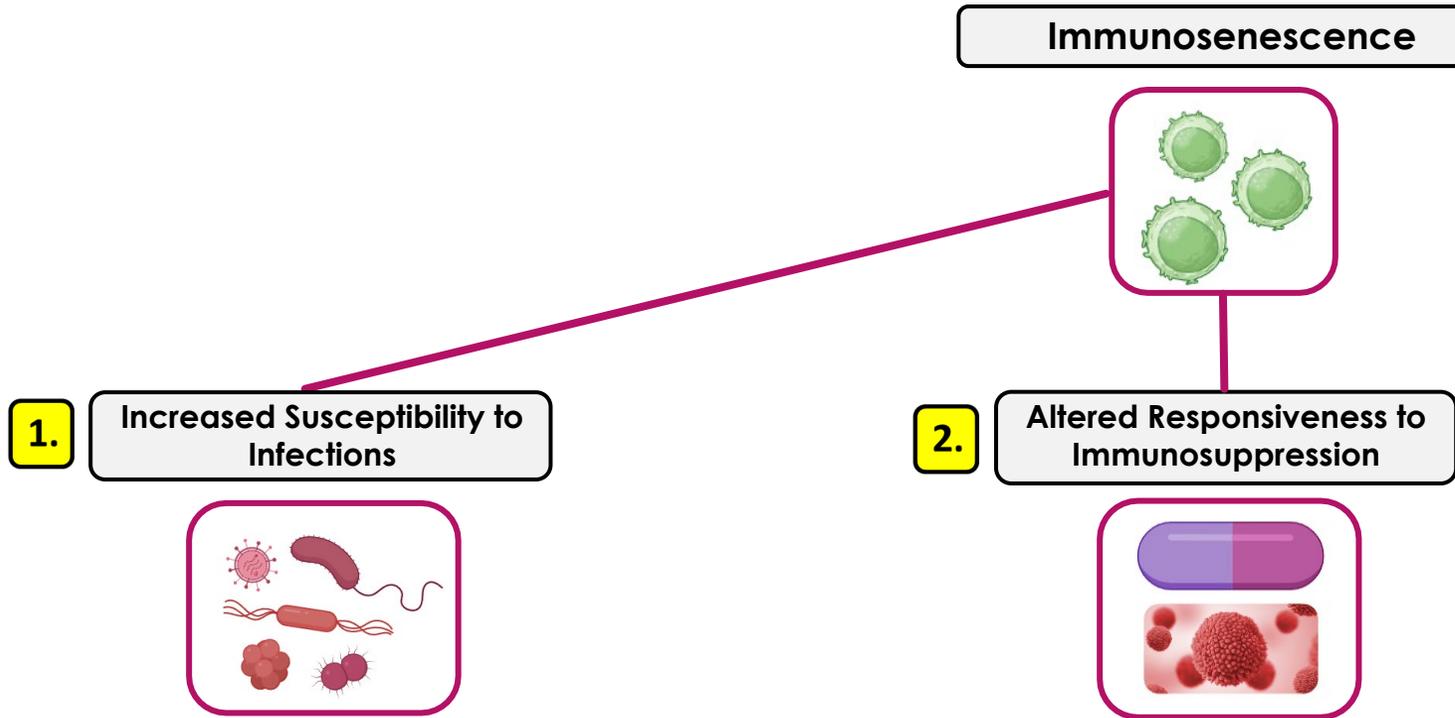


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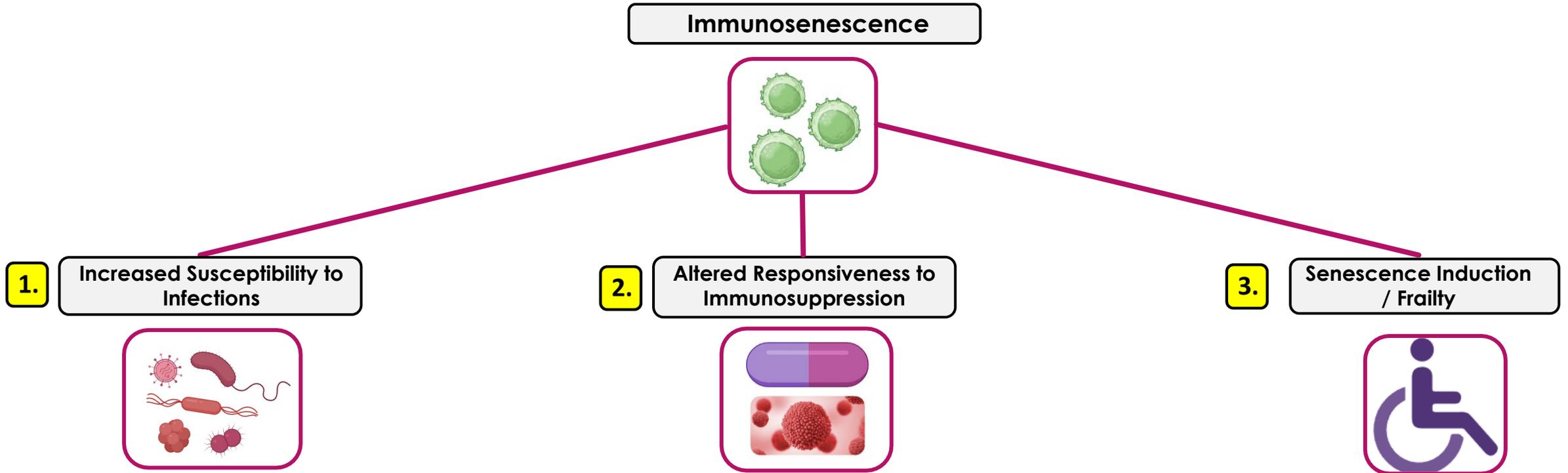
Increased Susceptibility to
Infections



Major Obstacles during Transplantation in the Elderly



Major Obstacles during Transplantation in the Elderly

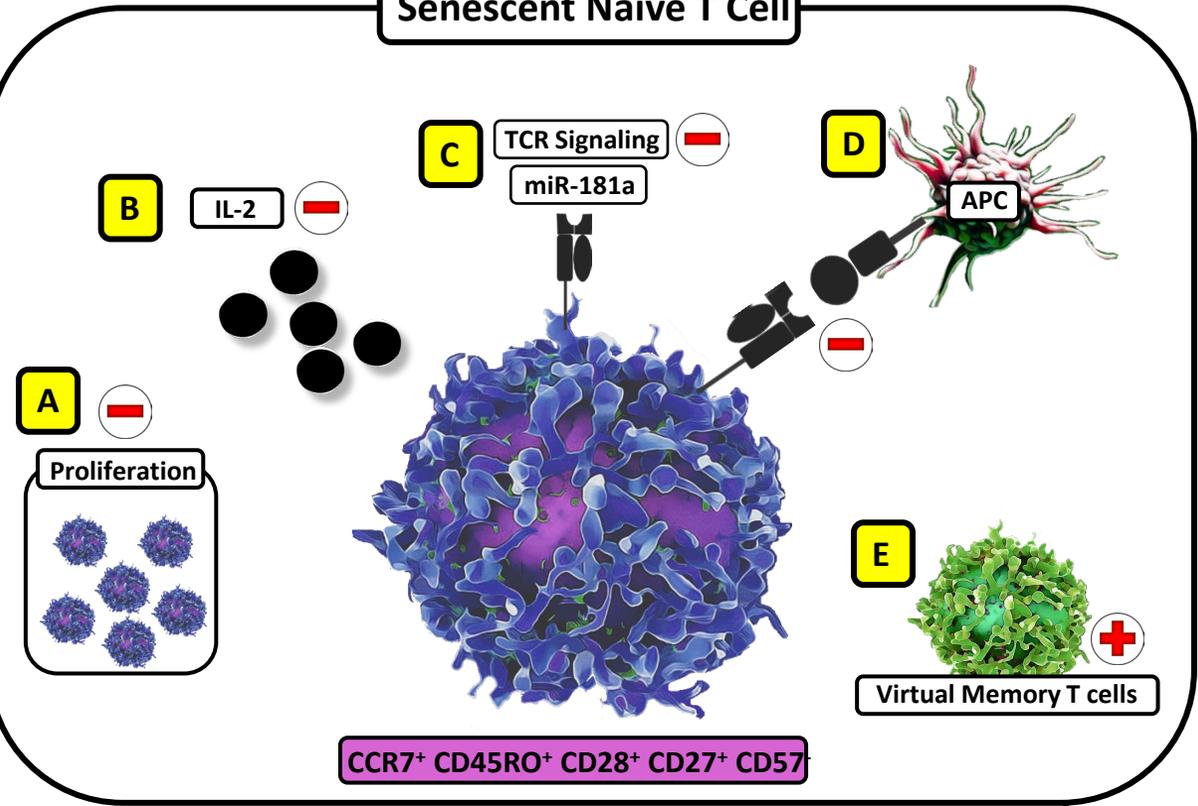




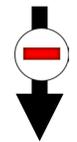
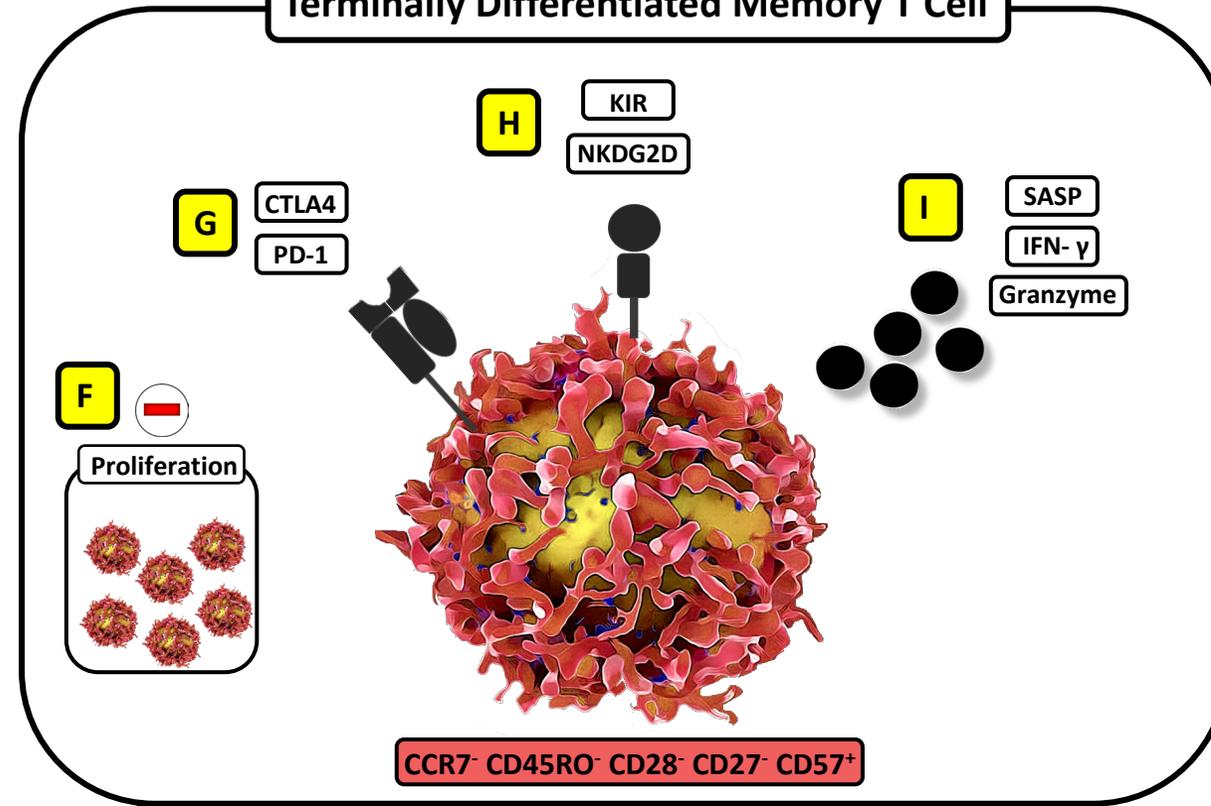
**T cell Aging contributes crucially
to these adverse Outcomes**

Old Recipient

Senescent Naive T Cell

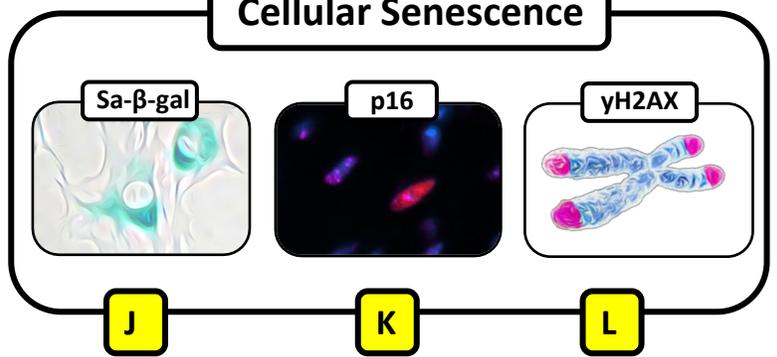


Terminally Differentiated Memory T Cell



Allo-Immune response
Pathogen Defense

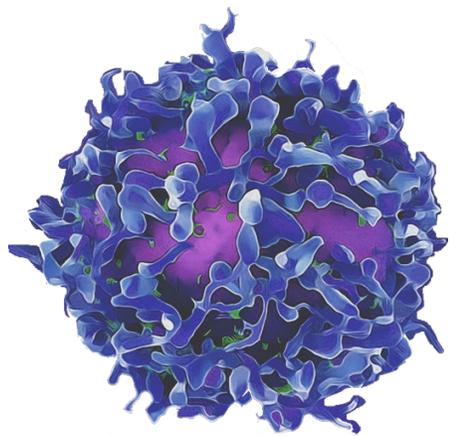
Cellular Senescence



Inflammaging
Senescence Induction

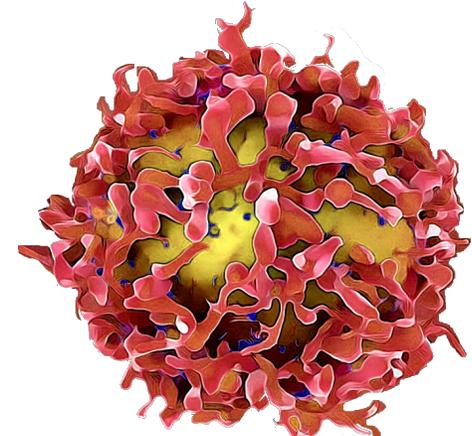
Old Recipient

Senescent Naive T Cell



CCR7⁺ CD45RO⁺ CD28⁺ CD27⁺ CD57⁻

Terminally Differentiated Memory T Cell



CCR7⁻ CD45RO⁻ CD28⁻ CD27⁻ CD57⁺

Cellular Senescence

Three panels illustrating cellular senescence markers:

- Sa-β-gal**: A micrograph showing blue-stained cells, indicating senescence.
- p16**: A fluorescence micrograph showing red and blue signals, indicating p16 expression.
- γH2AX**: A fluorescence micrograph showing blue and red signals, indicating DNA damage.

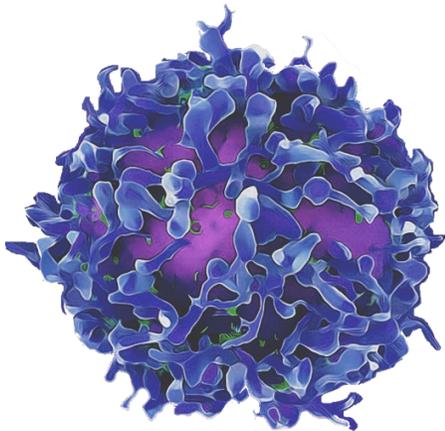
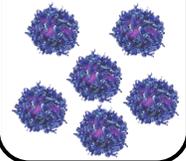
Old Recipient

Senescent Naive T Cell

A



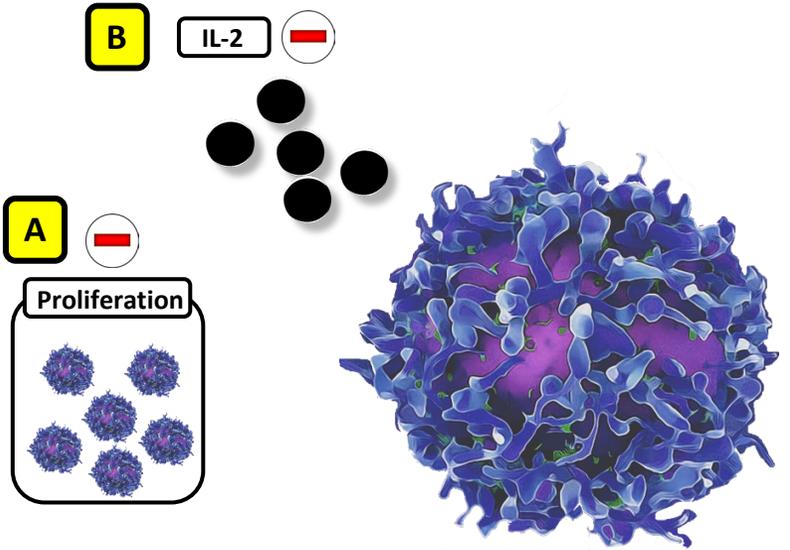
Proliferation



CCR7⁺ CD45RO⁺ CD28⁺ CD27⁺ CD57⁻

Old Recipient

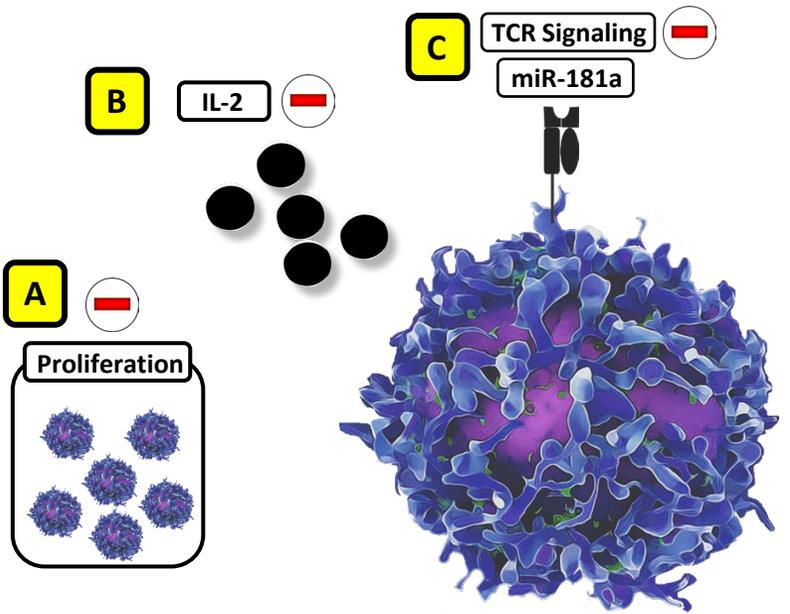
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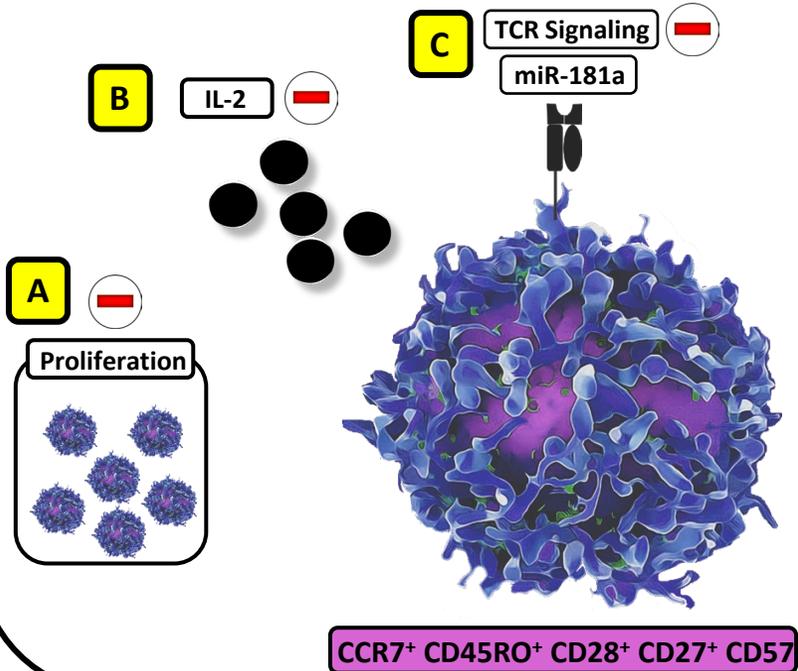
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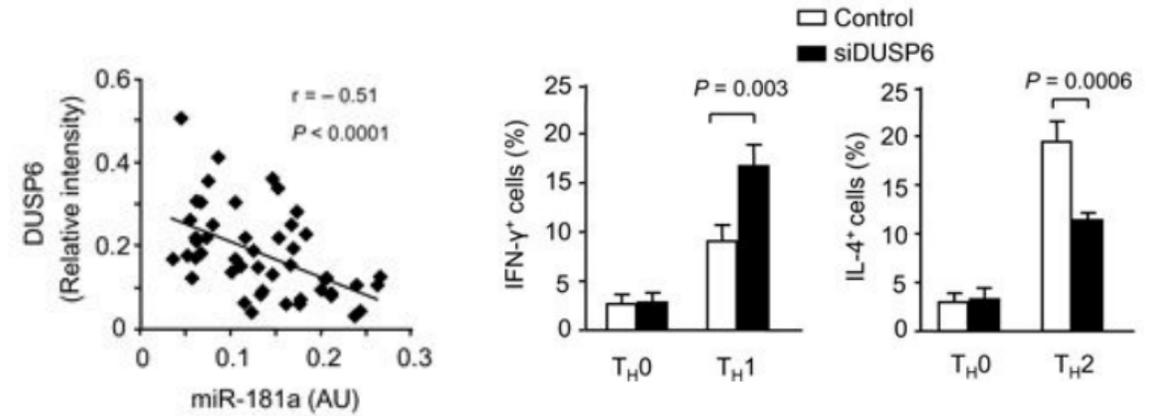
Senescent Naive T Cell



> *Nat Med.* 2012 Oct;18(10):1518-24. doi: 10.1038/nm.2963. Epub 2012 Sep 30.

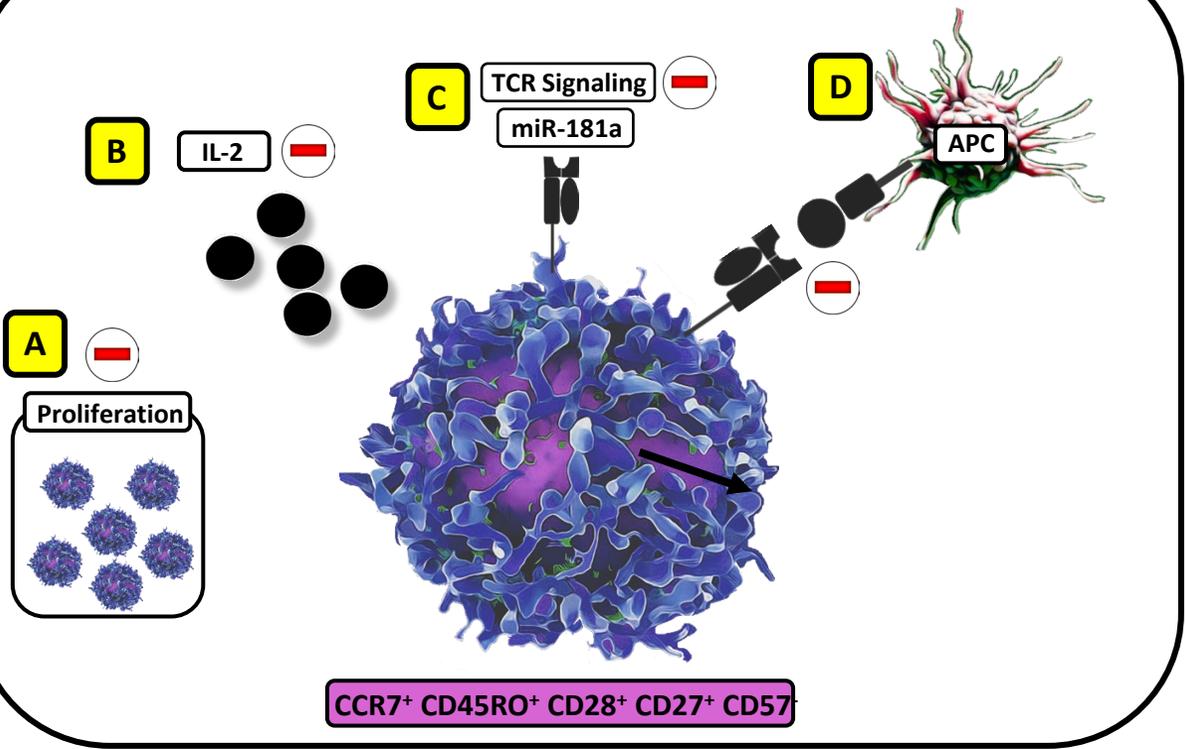
Decline in miR-181a expression with age impairs T cell receptor sensitivity by increasing DUSP6 activity

Guangjin Li¹, Mingcan Yu, Won-Woo Lee, Michael Tsang, Eswar Krishnan, Cornelia M Weyand, Jörg J Goronzy



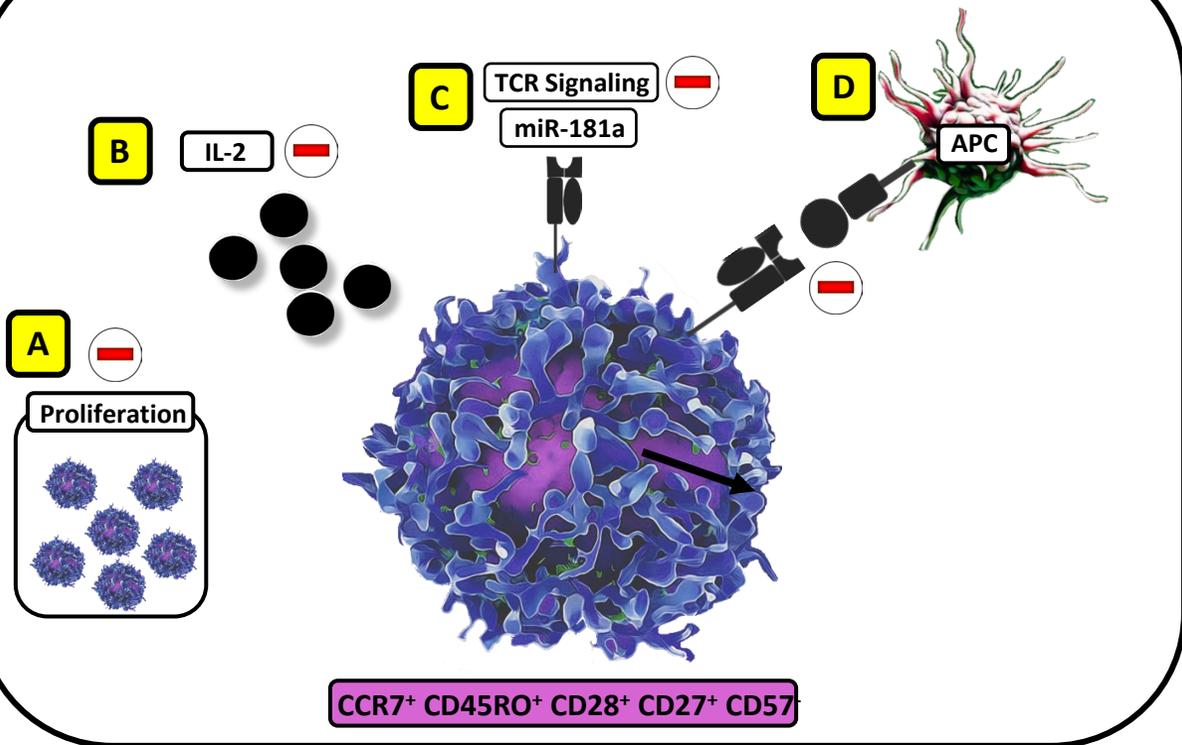
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Senescent Naive T Cell



Old Recipient

Senescent Naive T Cell



> *J Immunol.* 2001 Mar 1;166(5):3151-7. doi: 10.4049/jimmunol.166.5.3151.

Single-cell analyses reveal two defects in peptide-specific activation of naive T cells from aged mice

G G Garcia ¹, R A Miller

> *J Immunol.* 2002 Nov 1;169(9):5021-7. doi: 10.4049/jimmunol.169.9.5021.

Age-dependent defects in TCR-triggered cytoskeletal rearrangement in CD4⁺ T cells

Gonzalo G Garcia ¹, Richard A Miller

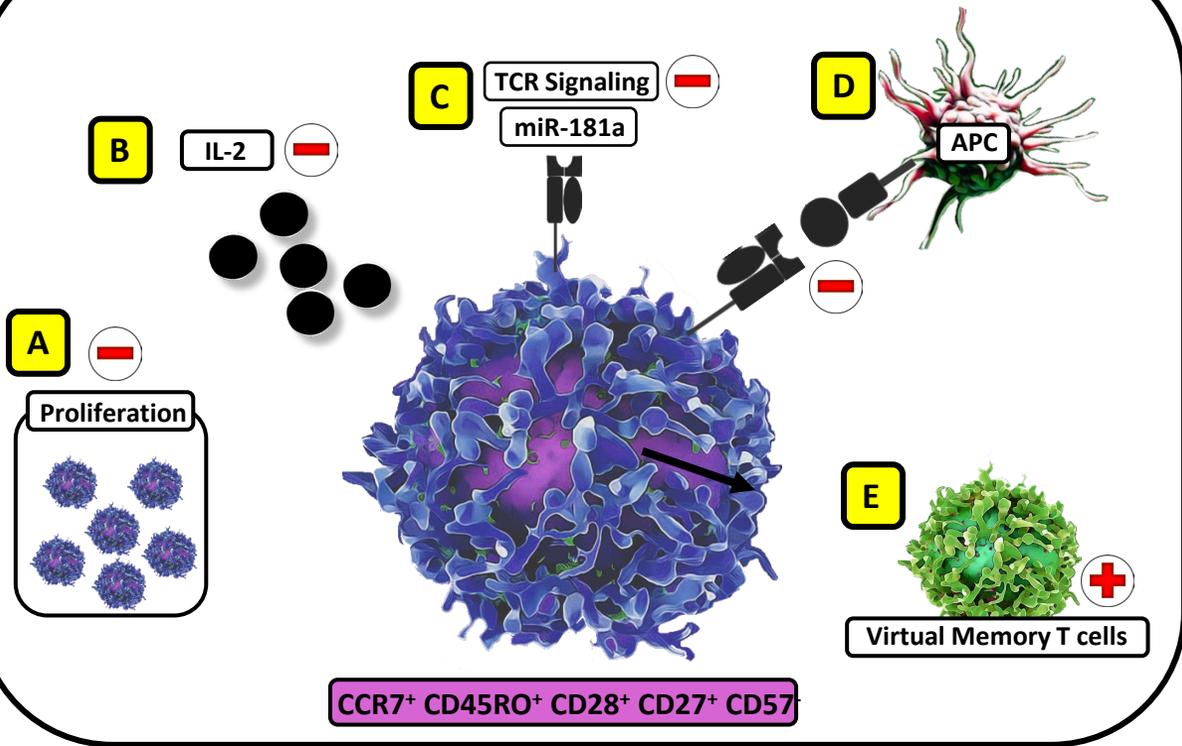
> *Int Immunol.* 2009 Nov;21(11):1277-89. doi: 10.1093/intimm/dxp094. Epub 2009 Sep 11.

Naive CD4 T cells from aged mice show enhanced death upon primary activation

Hamid Mattoo ¹, Matthew Faulkner, Usha Kandpal, Rituparna Das, Virginia Lewis, Anna George, Satyajit Rath, Jeannine M Durdik, Vineeta Bal

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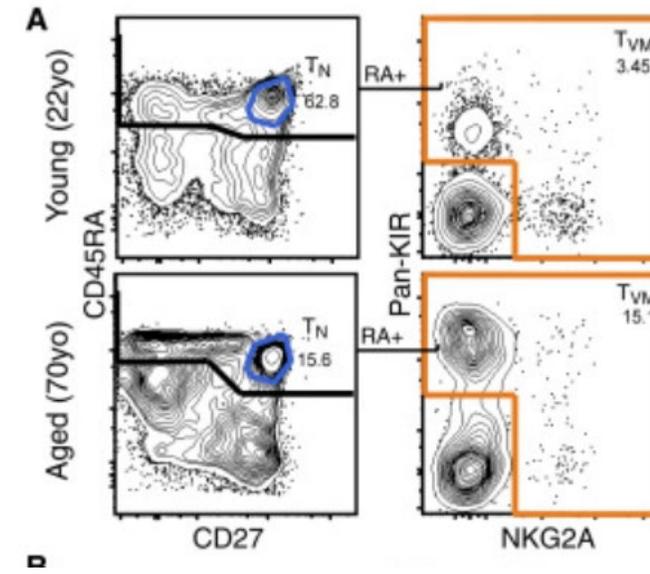
Senescent Naive T Cell



> Cell Rep. 2018 Jun 19;23(12):3512-3524. doi: 10.1016/j.celrep.2018.05.057.

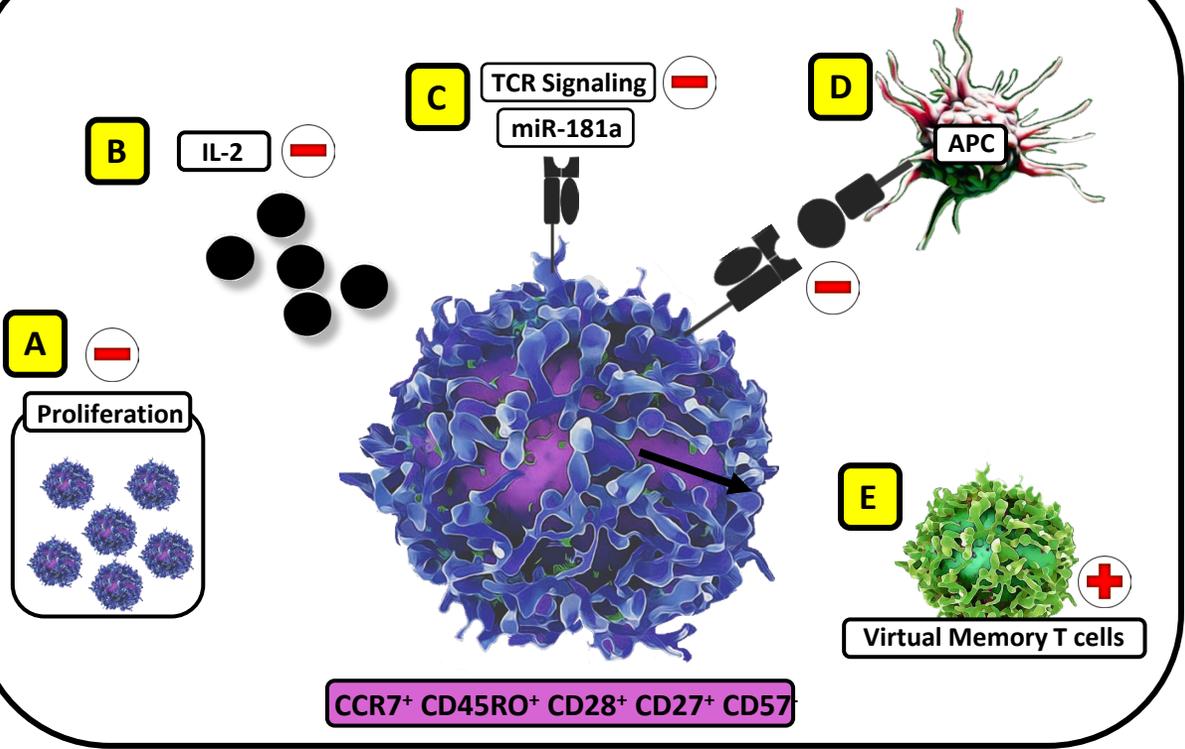
Age-Related Decline in Primary CD8⁺ T Cell Responses Is Associated with the Development of Senescence in Virtual Memory CD8⁺ T Cells

Kylie M Quinn¹, Annette Fox², Kim L Harland², Brendan E Russ³, Jasmine Li³, Thi H O Nguyen², Liyen Loh², Moshe Olshanky³, Haroon Naeem⁴, Kirill Tsyganov⁴, Florian Wiede⁵, Rosela Webster⁶, Chantelle Blyth⁶, Xavier Y X Sng⁶, Tony Tiganis⁵, David Powell⁴, Peter C Doherty⁷, Stephen J Turner⁸, Katherine Kedzierska², Nicole L La Gruta⁹

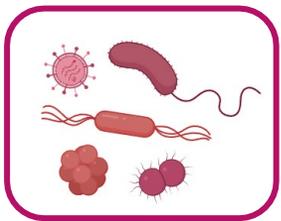


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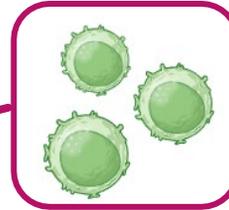


Increased Susceptibility to Infections



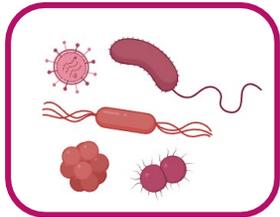
Major Obstacles during Transplantation in the Elderly

Immunosenescence



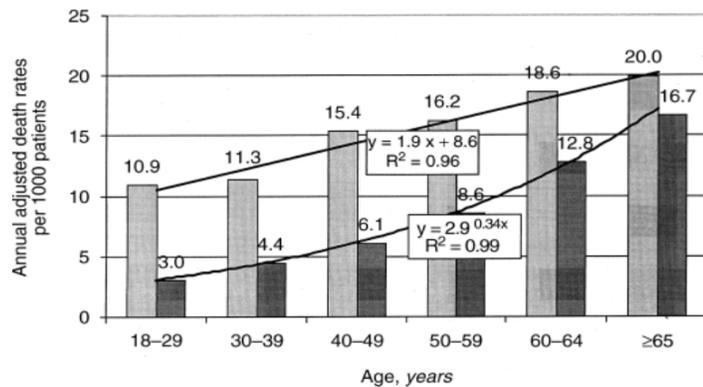
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Increased Susceptibility to Infections



Immunosenescence in Old Recipients confers an Increased Susceptibility to Infections

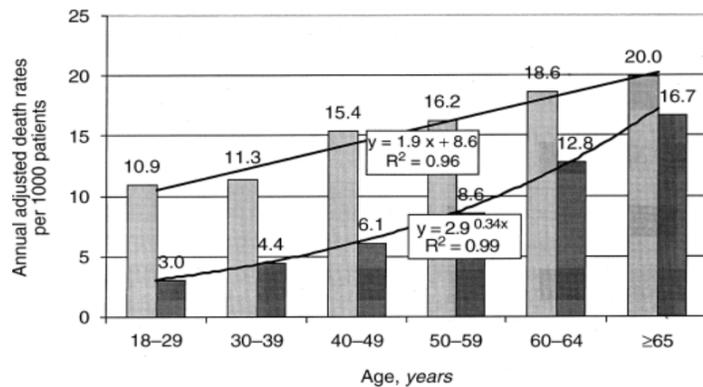
Recipient Age - Infections



Exponentially increased risk of infectious death in older renal transplant recipients

Immunosenescence in Old Recipients confers an Increased Susceptibility to Infections

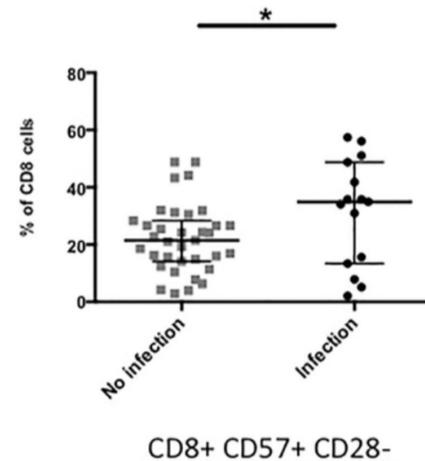
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Exponentially increased risk of infectious death in older renal transplant recipients

H U Meier-Kriesche¹, A O Ojo, J A Hanson, B Kaplan

Immunosenescence - Infections

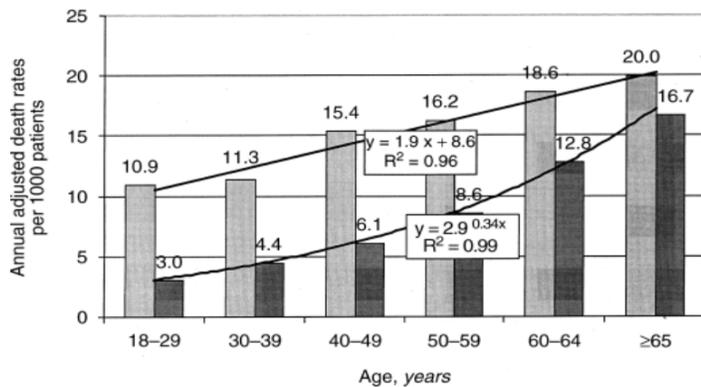


Increased T cell immunosenescence and accelerated maturation phenotypes in older kidney transplant recipients

J M Schaeferman¹, M Rossetti², T Sidwell², V Groysberg², G Sunga², Y Korin², E Liang³, X Zhou⁴, B Abdalla⁵, E Lum⁵, S Bunnapradist⁵, T Pham⁵, G Danovitch⁵, E F Reed²

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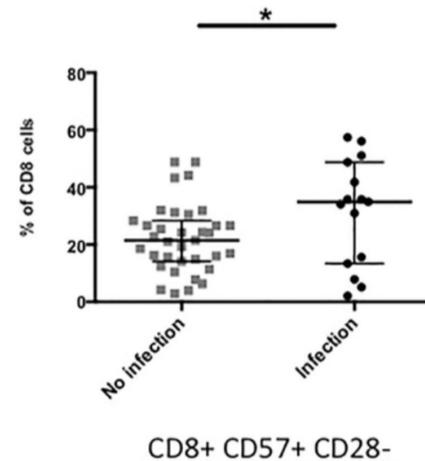
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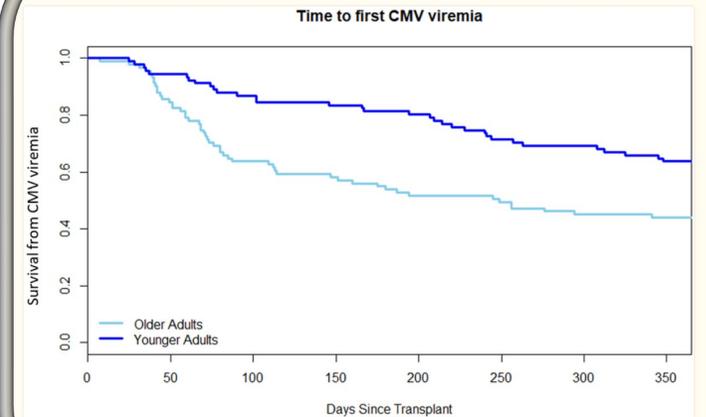
Immunosenescence - Infections



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Recipient Age - CMV Reactivation

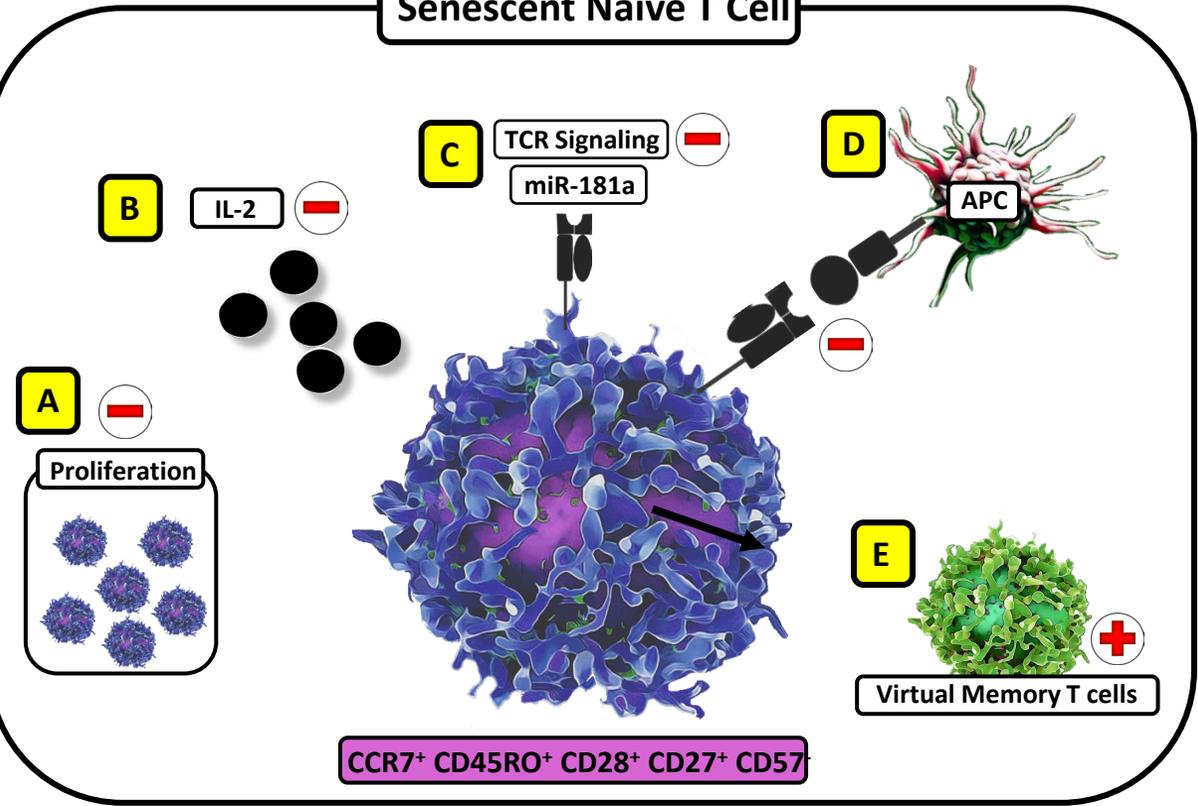


Age matters: older age as a risk factor for CMV reactivation in the CMV serostatus-positive kidney transplant recipient

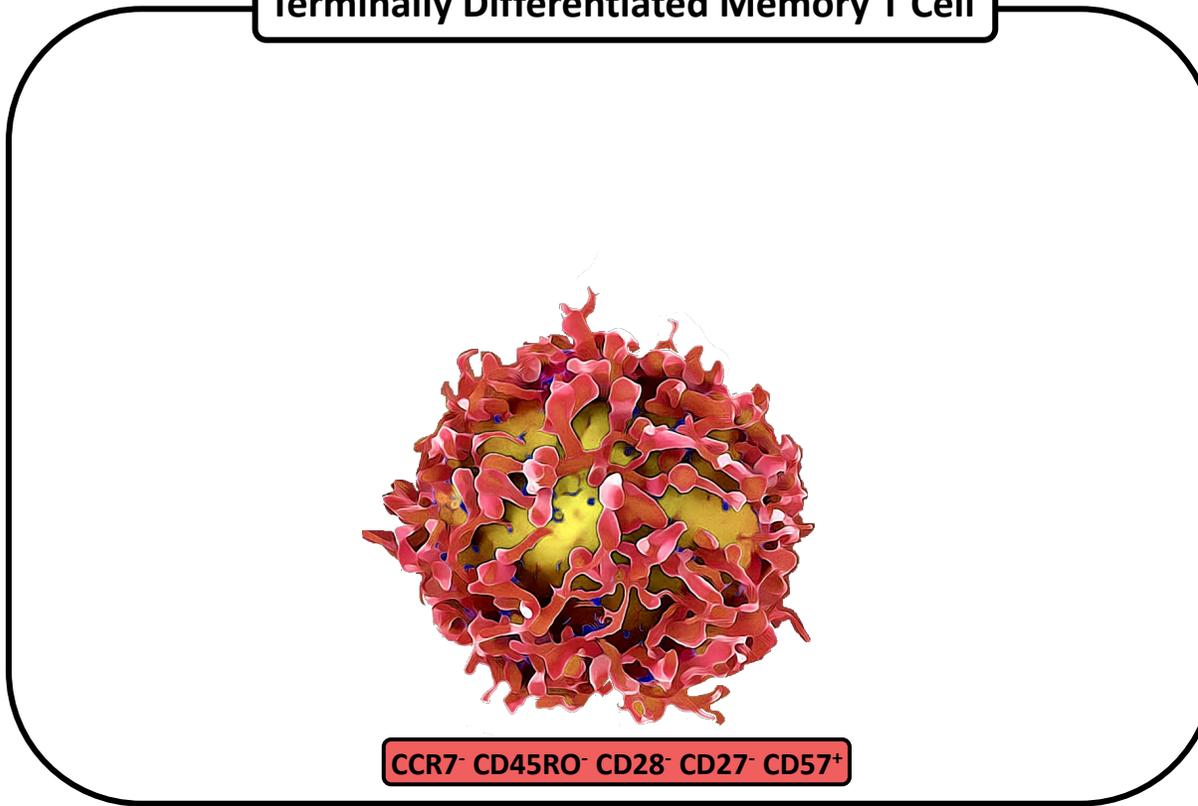
Marion Hemmersbach-Miller^{1,2}, Barbara D Alexander³, Carl F Pieper⁴, Kenneth E Schumacher^{5,6}

Old Recipient

Senescent Naive T Cell

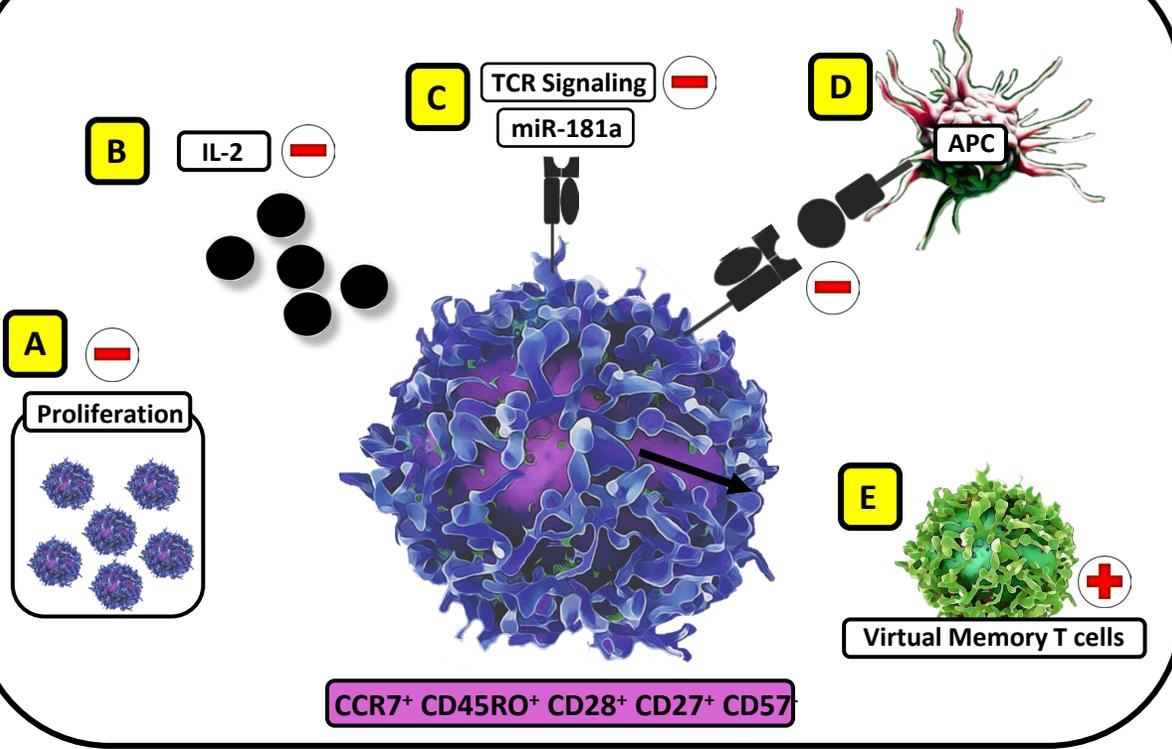


Terminally Differentiated Memory T Cell

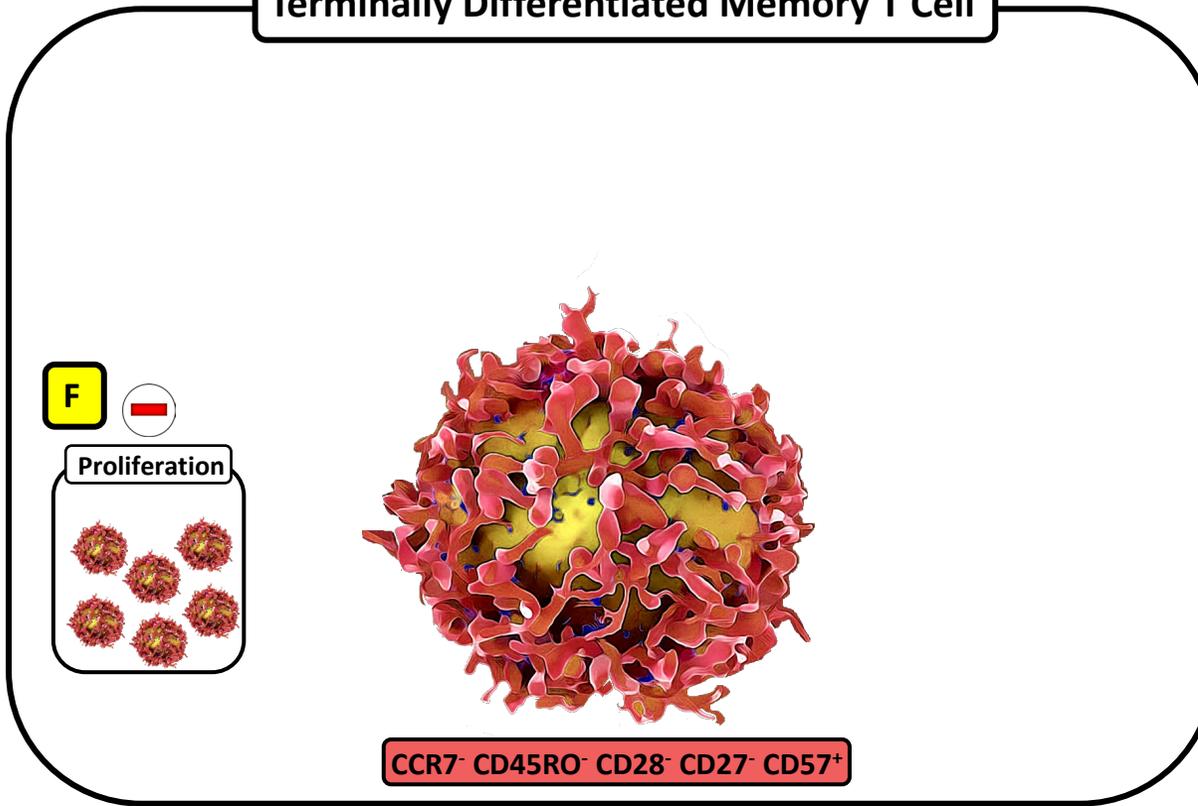


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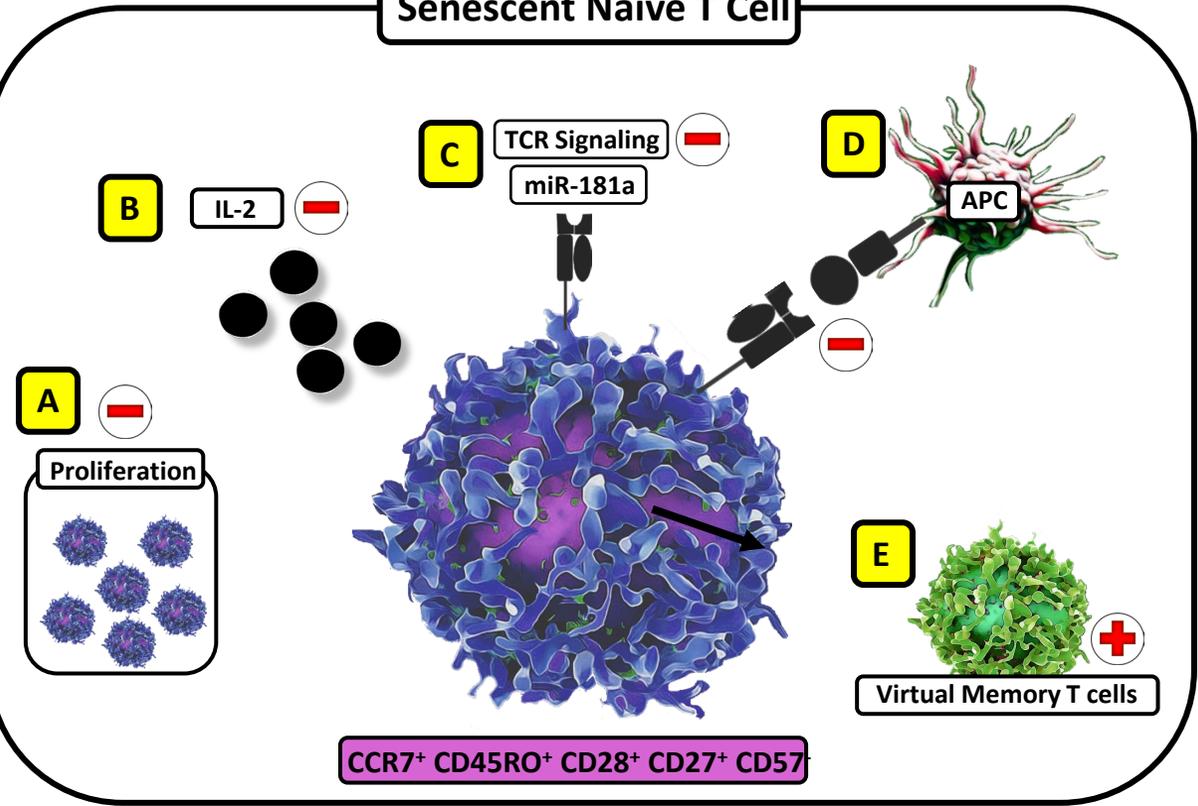


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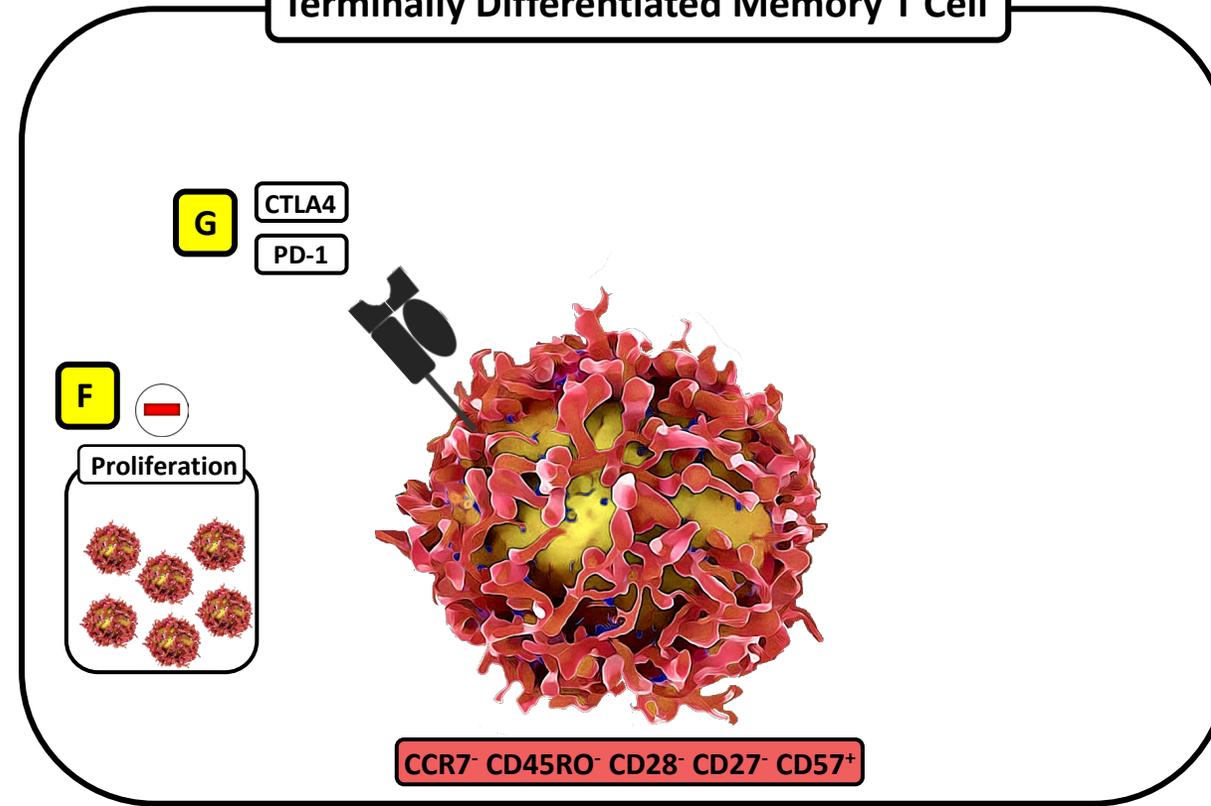


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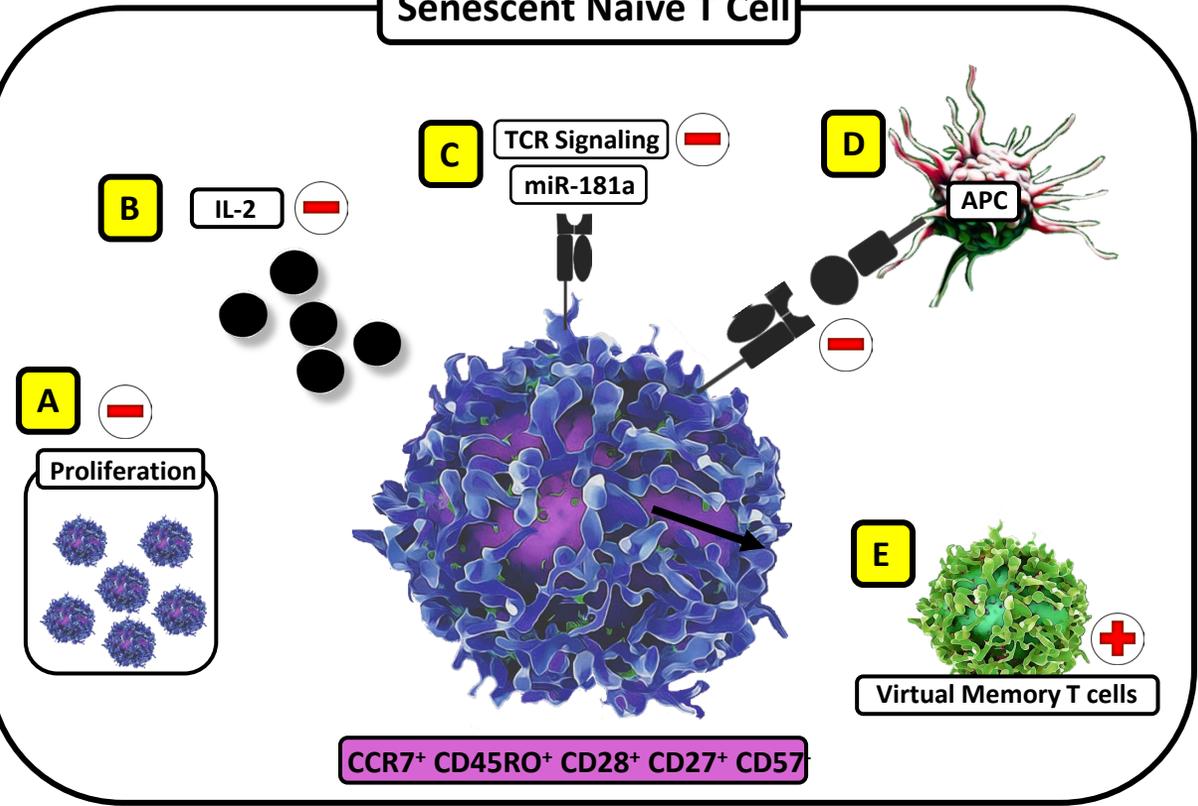


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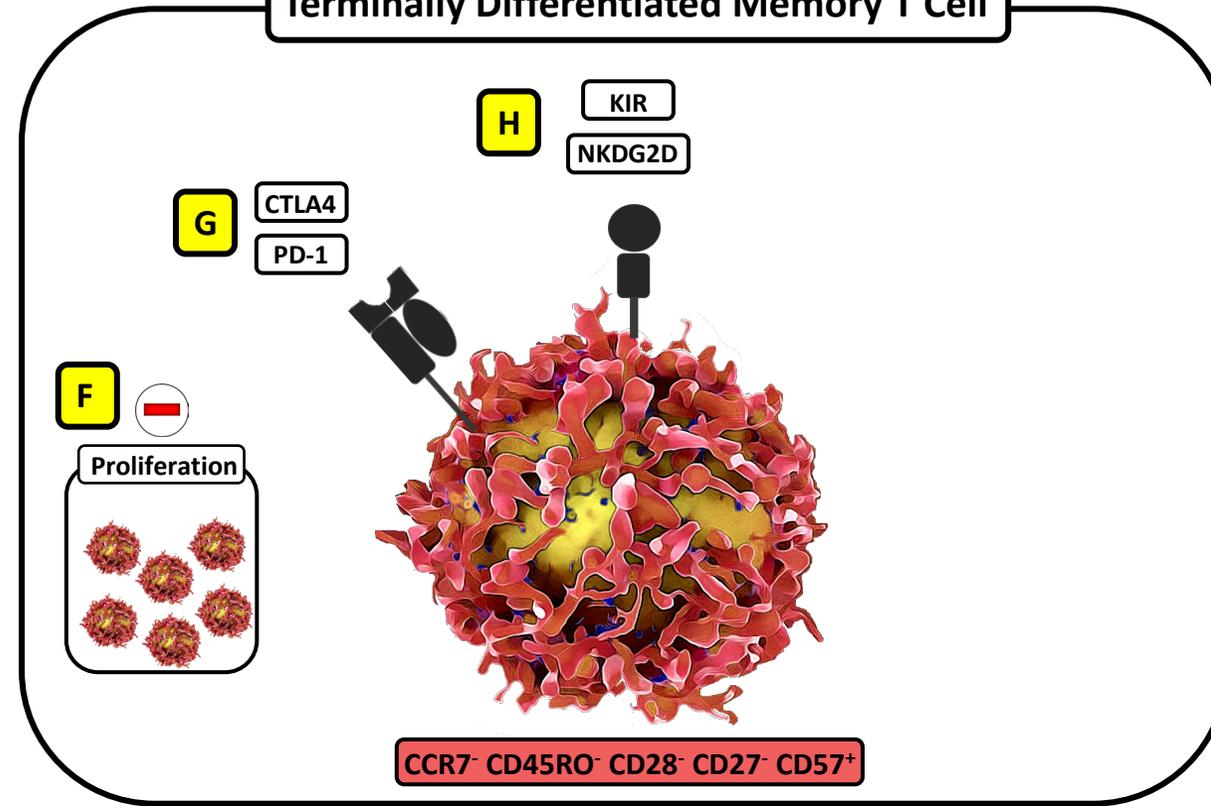


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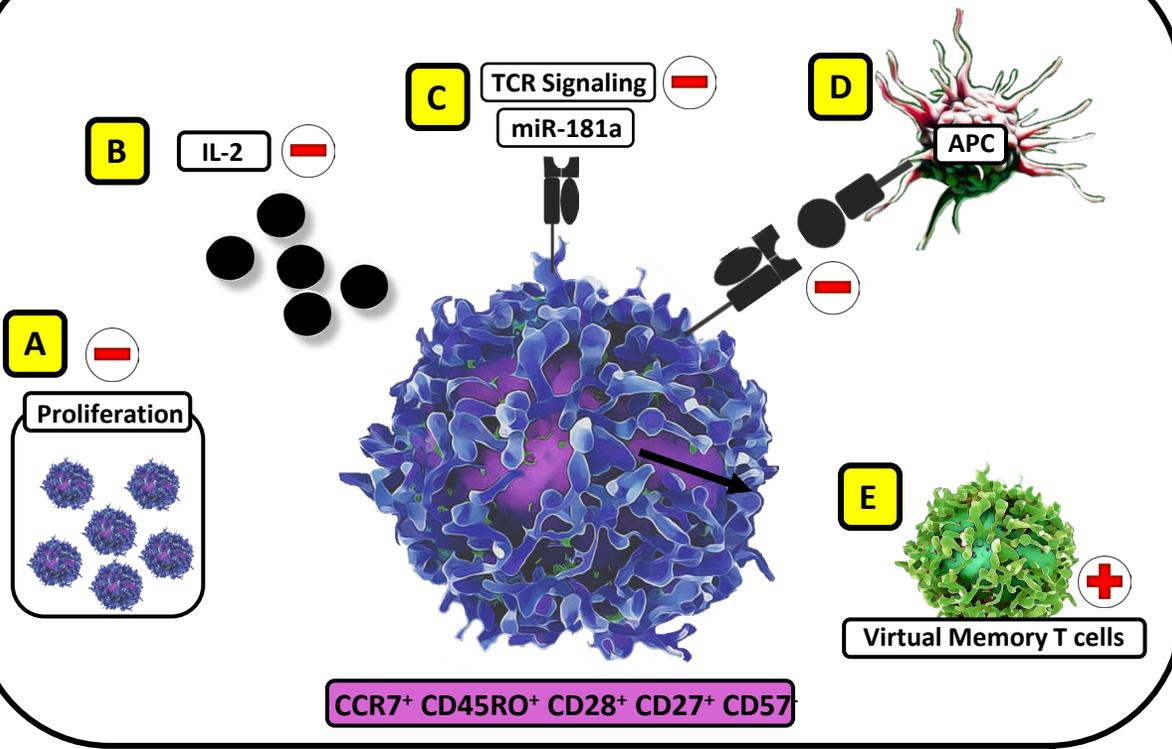


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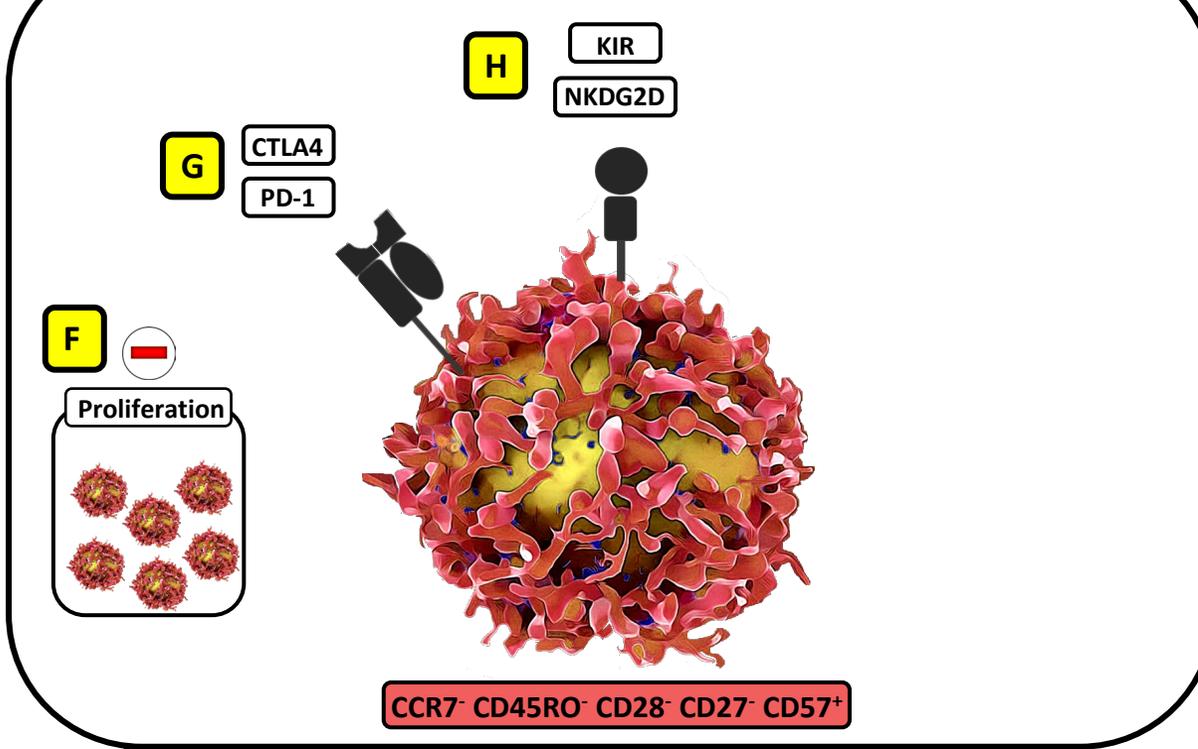


Old Recipient

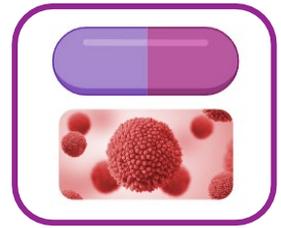
Senescent Naive T Cell



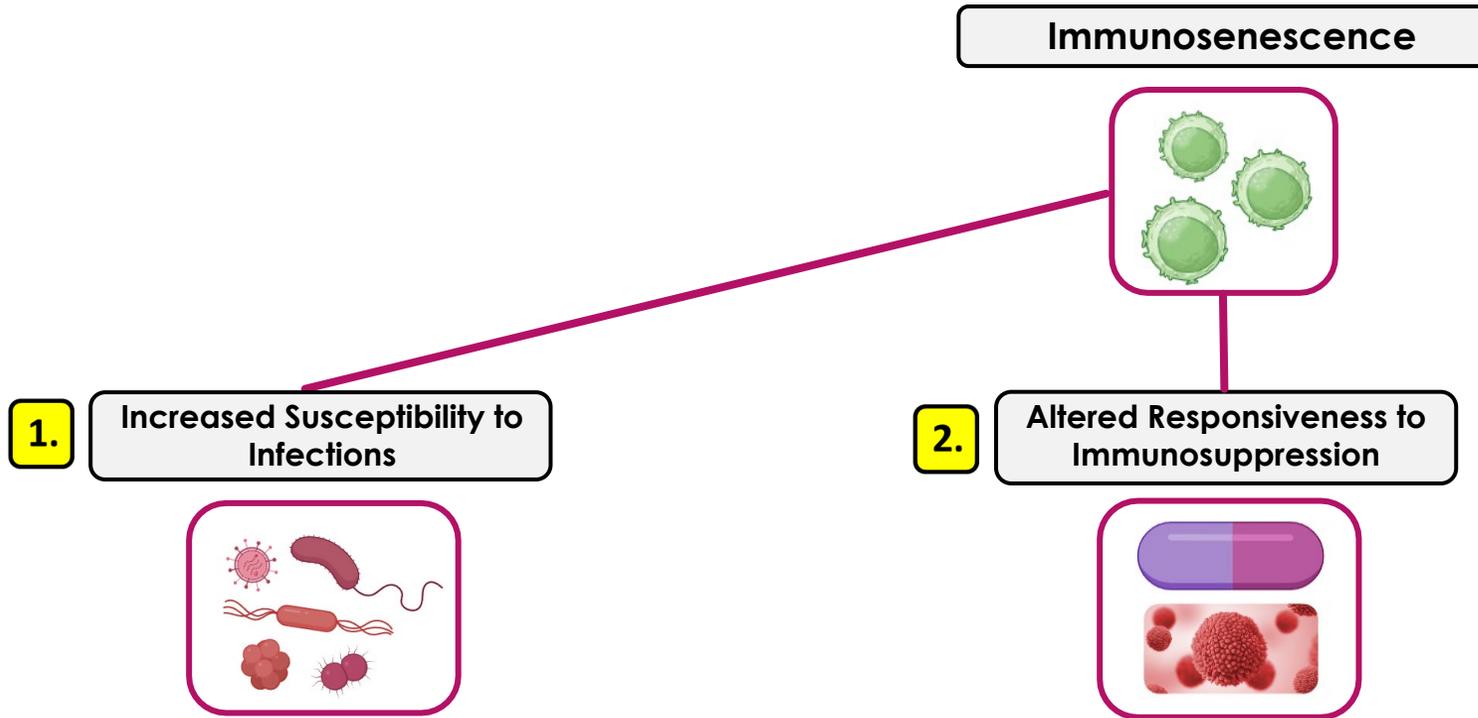
Terminally Differentiated Memory T Cell



Altered Responsiveness to Immunosuppression

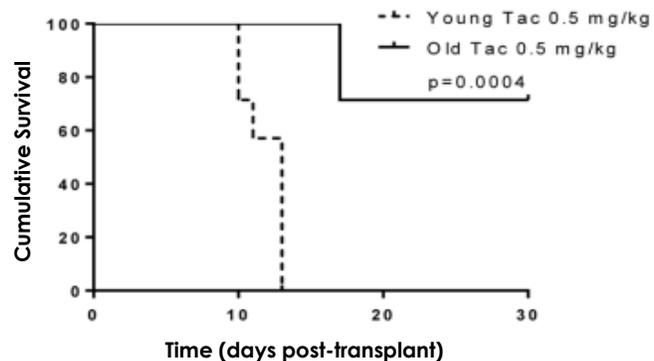


Major Obstacles during Transplantation in the Elderly



Immunosenescence in Old Recipients Alters the Responsiveness to Immunosuppression

Tacrolimus – CD4⁺ T cell Suppression

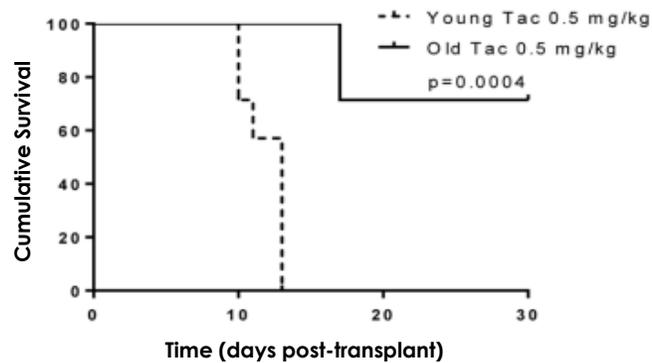


Age-Dependent Metabolic and Immunosuppressive Effects of Tacrolimus

F Krenzien^{1,2}, M Quante^{1,3}, T Heinbokenl^{1,4}, M Seyda^{1,5}, K Minami^{1,6}, H Uehara^{1,6}, H R C Biefer^{1,7}, J M Schuitenmaker¹, S Gabardi⁸, K Splith², M Schmelzle², A K Petrides⁹, H Azuma⁶, J Pratschke², X C Li¹⁰, A ElKhal¹, S G Tullius¹

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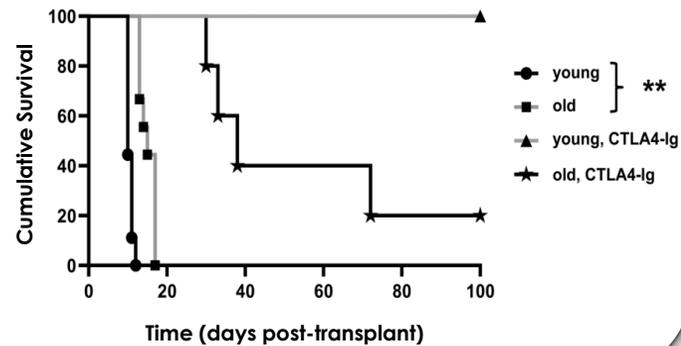
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CTLA4-Ig – CD28⁺ T cell Suppression

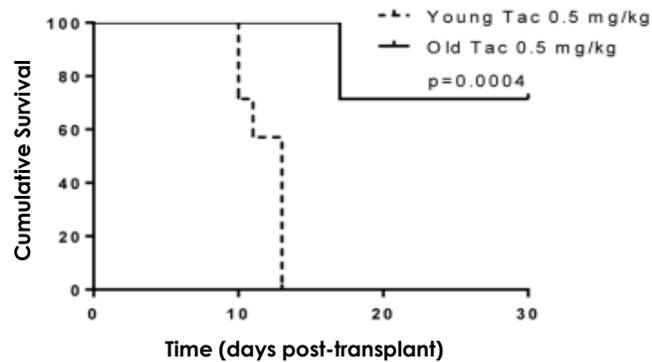


CTLA4-Ig prolongs graft survival specifically in young but not old mice

Timm Heinbokenl^{1,2}, Markus Quante^{1,3}, Jasper Iske^{1,4}, Yeqi Nian¹, Ryoichi Maenosono^{1,5}, Koichiro Minami^{1,5}, Yang Liu^{1,6}, Haruhito Azuma⁵, Abdallah ElKhal¹, Stefan G Tullius¹

Immunosenescence in Old Recipients Alters the Responsiveness to Immunosuppression

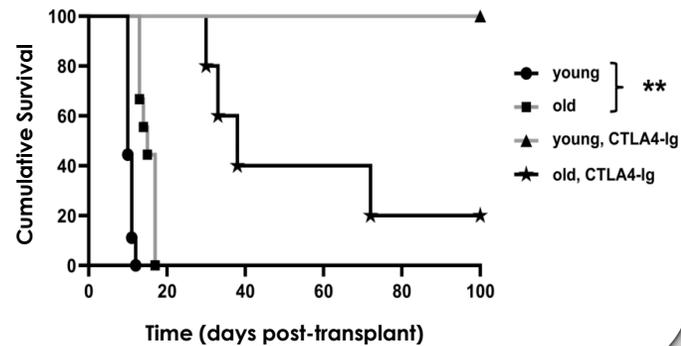
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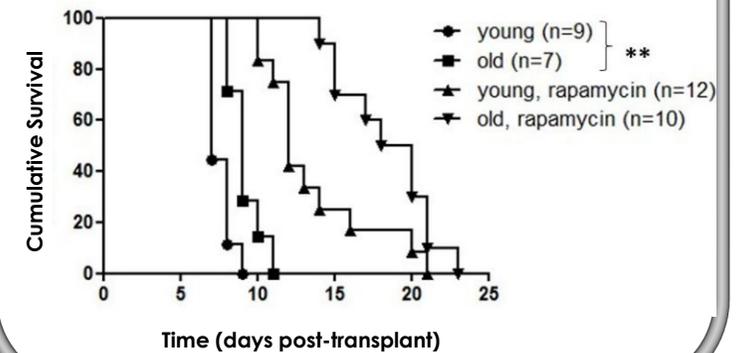
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Rapamycin – Tr1 Cell Induction

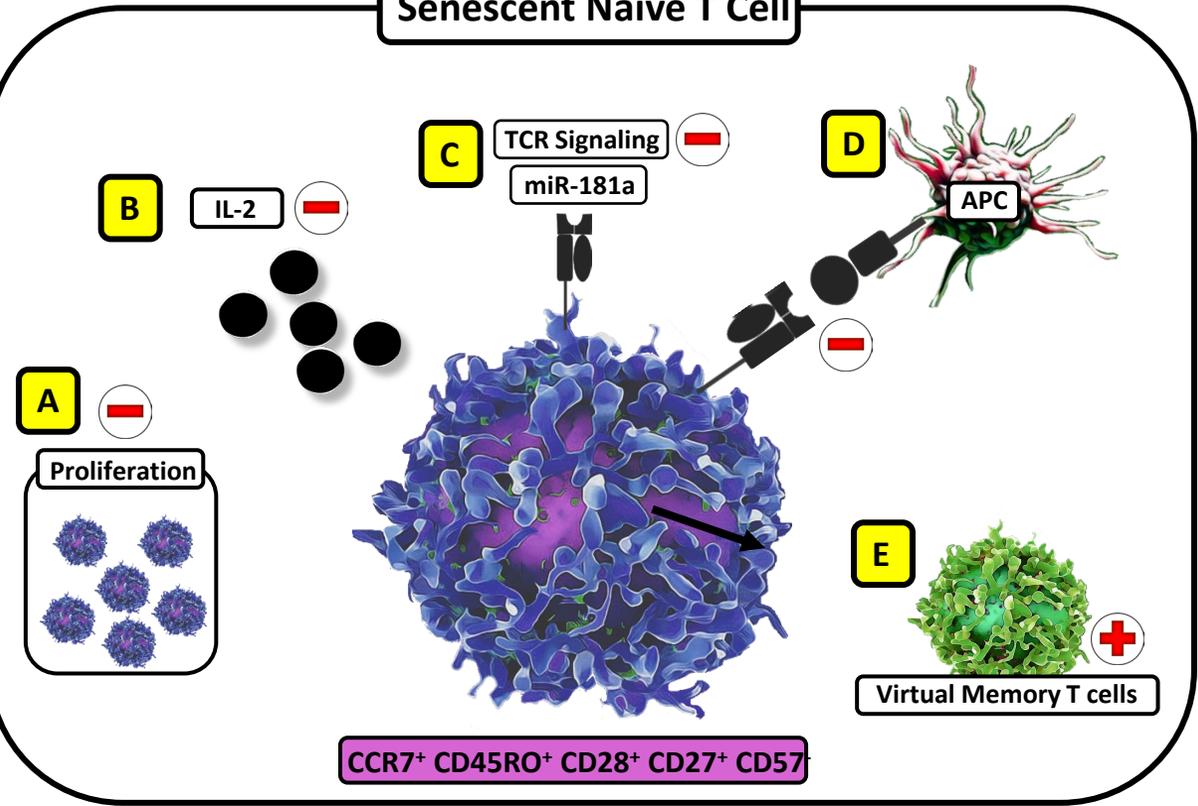


Rapamycin Prolongs Graft Survival and Induces CD4⁺IFN- γ +IL-10⁺ Regulatory Type 1 Cells in Old Recipient Mice

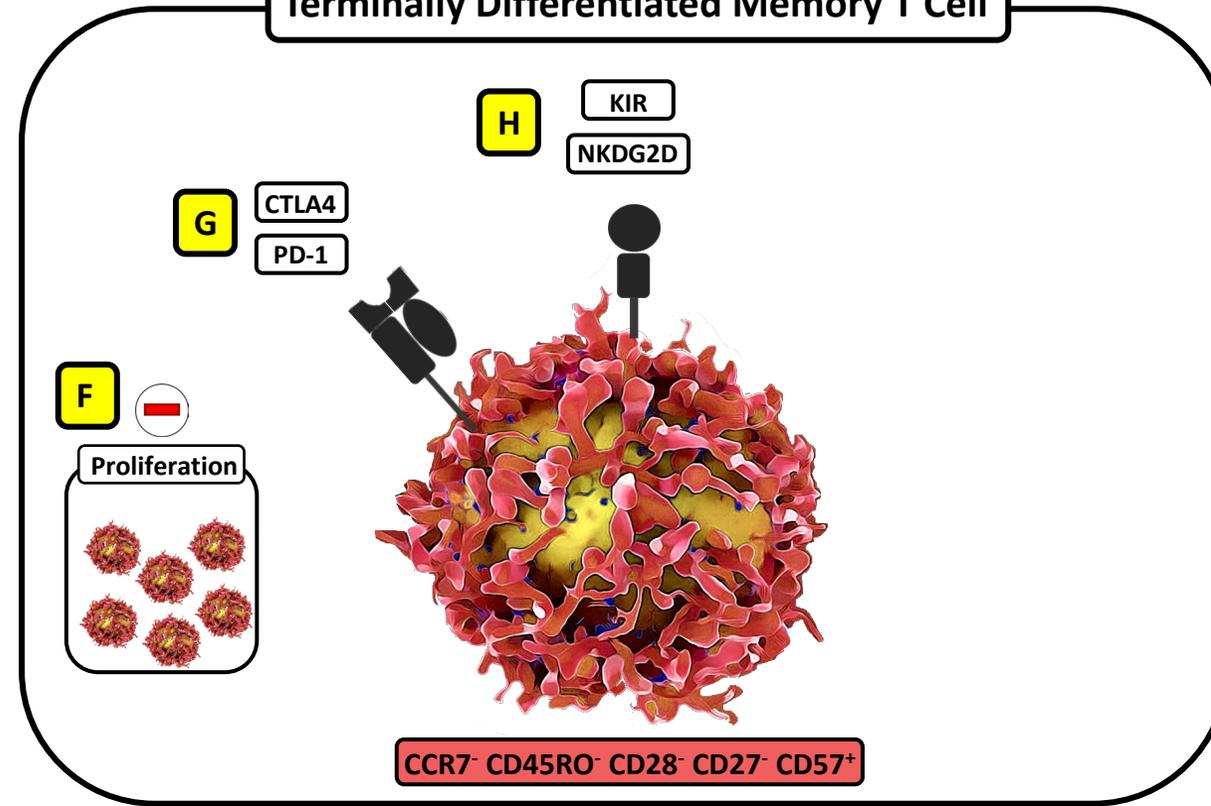
Markus Quante^{1,2}, Timm Heinbokenl^{1,3}, Karoline Edtinger^{1,4}, Koichiro Minami^{1,5}, Hirofumi Uehara⁵, Yeqi Nian¹, Haruhito Azuma⁴, Reza Abdi⁶, Abdallah ElKhal¹, Stefan G Tullius¹

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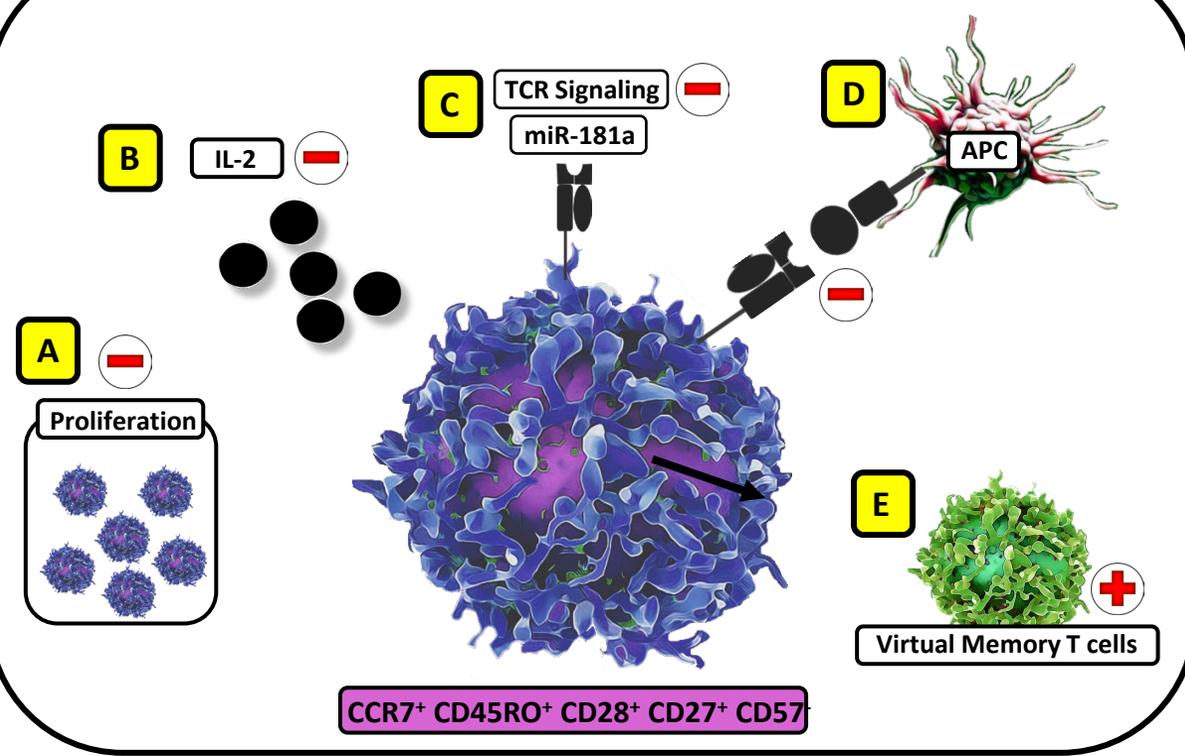


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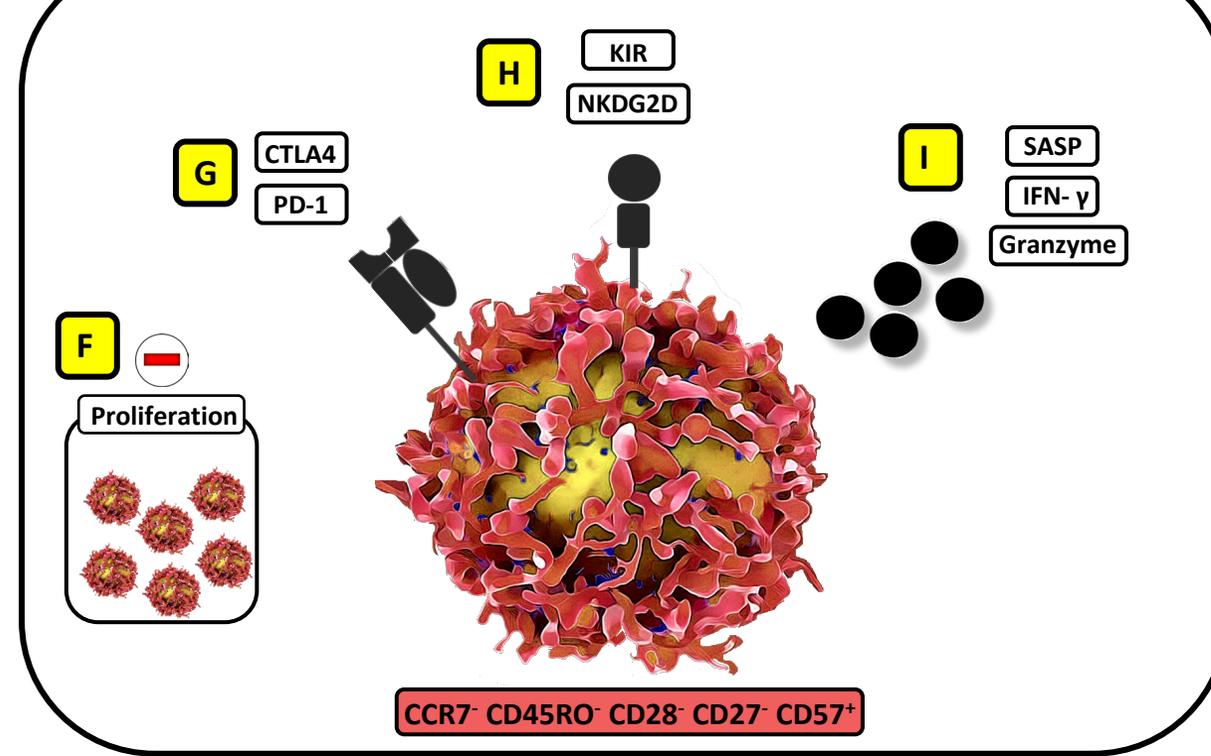


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Terminally Differentiated Memory T Cell

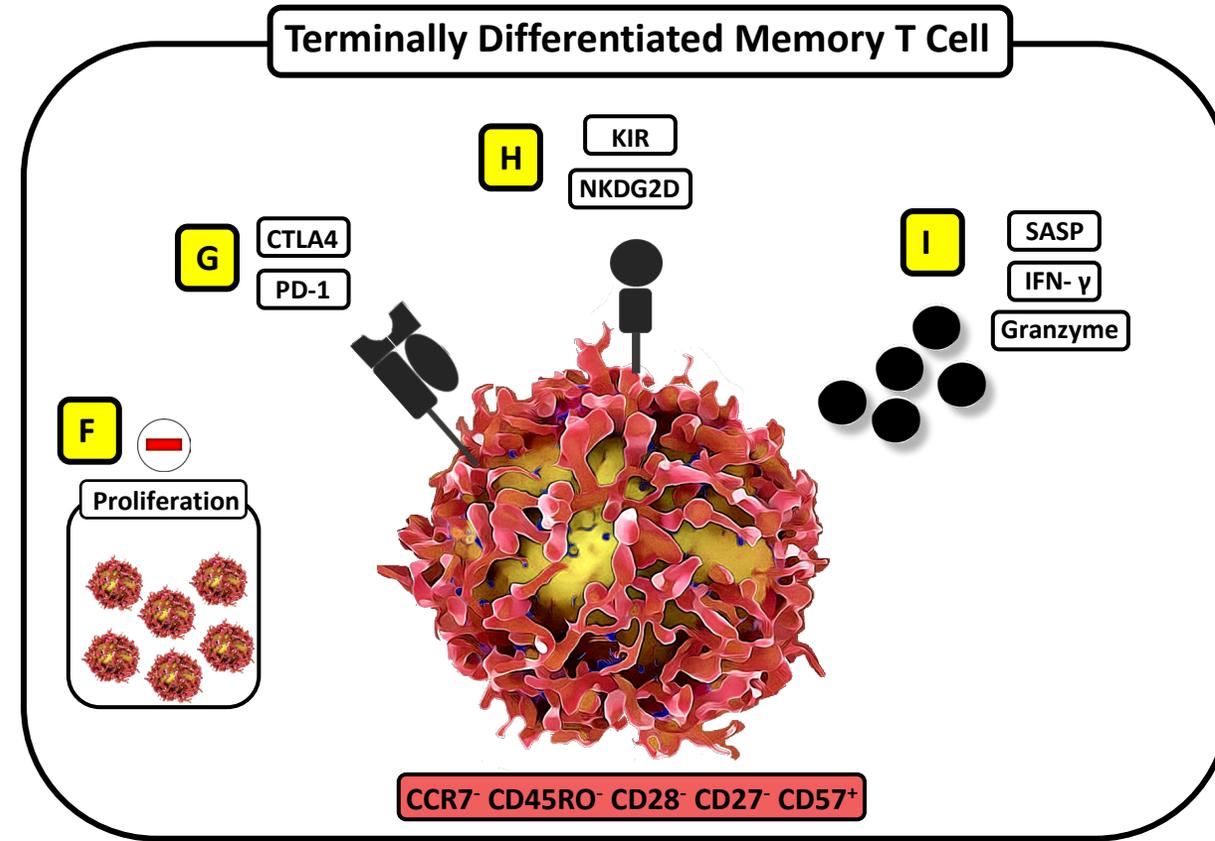
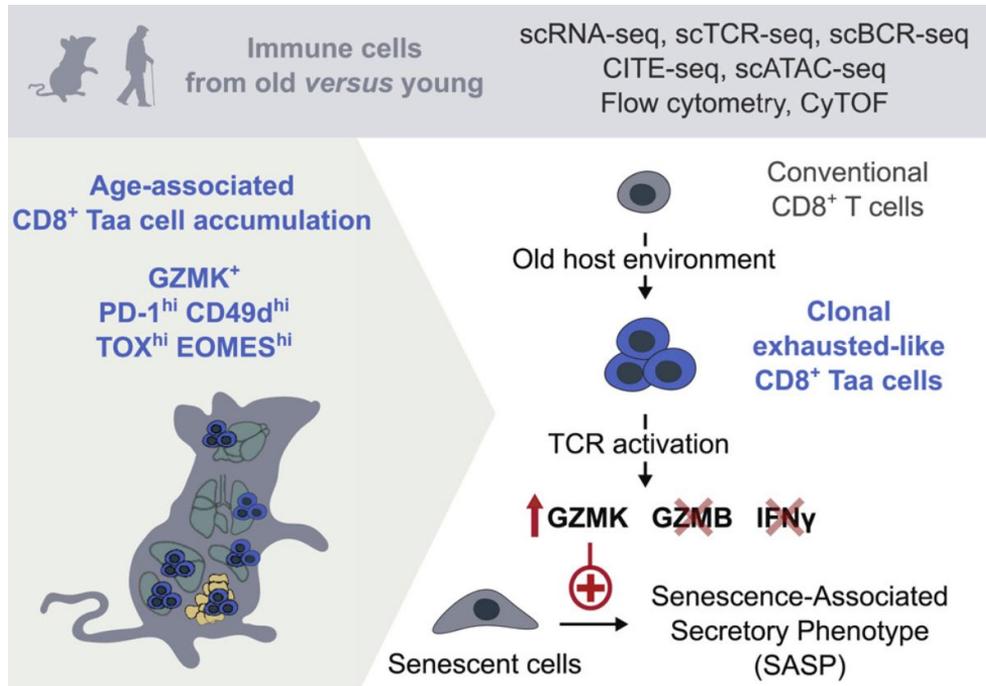


Old Recipient

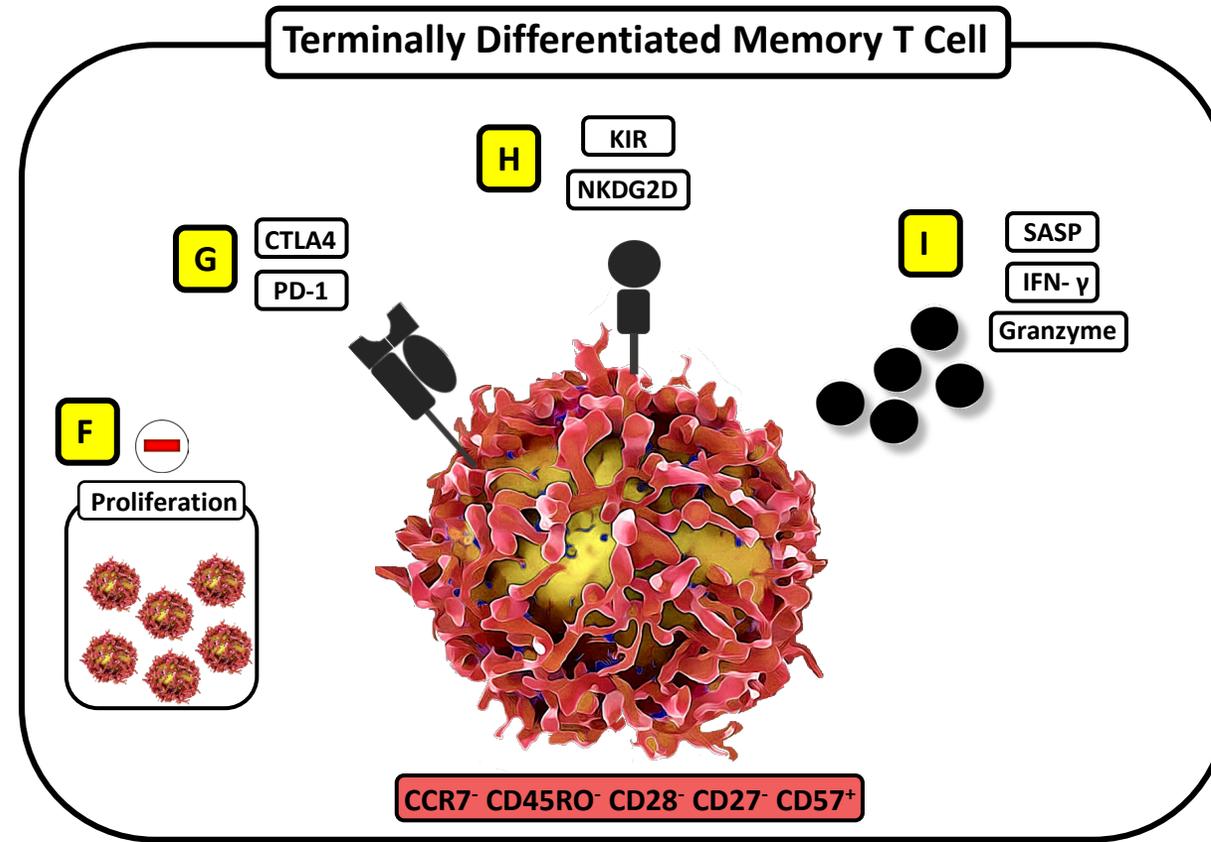
> *Immunity*. 2021 Jan 12;54(1):99-115.e12. doi: 10.1016/j.immuni.2020.11.005. Epub 2020 Dec 2.

Comprehensive Profiling of an Aging Immune System Reveals Clonal GZMK⁺ CD8⁺ T Cells as Conserved Hallmark of Inflammaging

Denis A Mogilenko¹, Oleg Shpynov², Prabhakar Sairam Andhey¹, Laura Arthur¹, Amanda Swain¹, Ekaterina Esaulova¹, Simone Brioschi¹, Irina Shchukina¹, Martina Kerndl³, Monika Bambouskova¹, Zhangting Yao⁴, Anwasha Laha¹, Konstantin Zaitsev⁵, Samantha Burdess¹, Susan Gillfilan¹, Sheila A Stewart⁴, Marco Colonna¹, Maxim N Artyomov⁶



Old Recipient

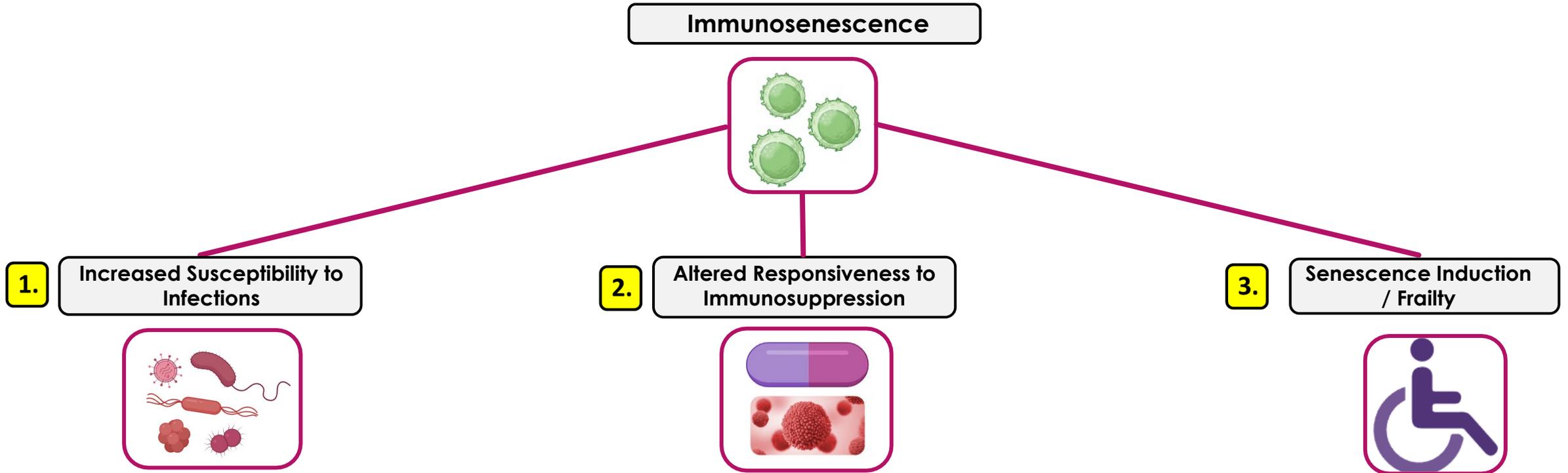


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Senescence Induction / Frailty

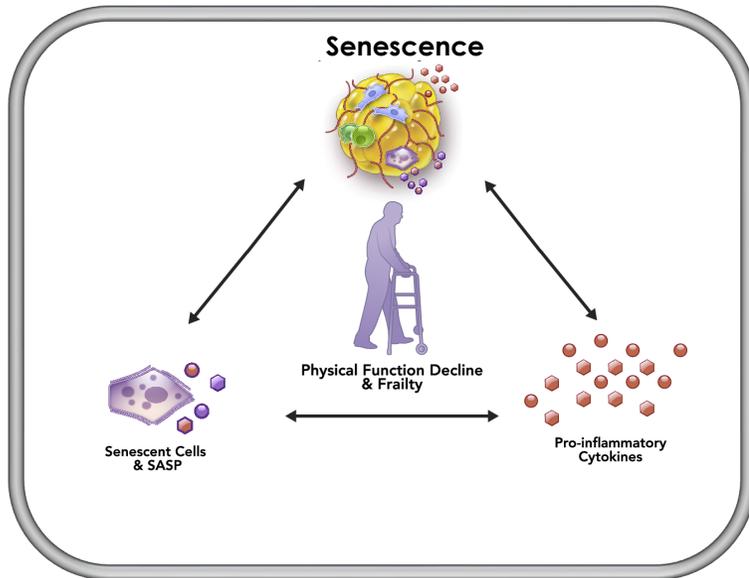


Major Obstacles during Transplantation in the Elderly



Older Recipients display Frailty Leading to Compromised Recipient Outcomes

Cellular Senescence Induces Frailty

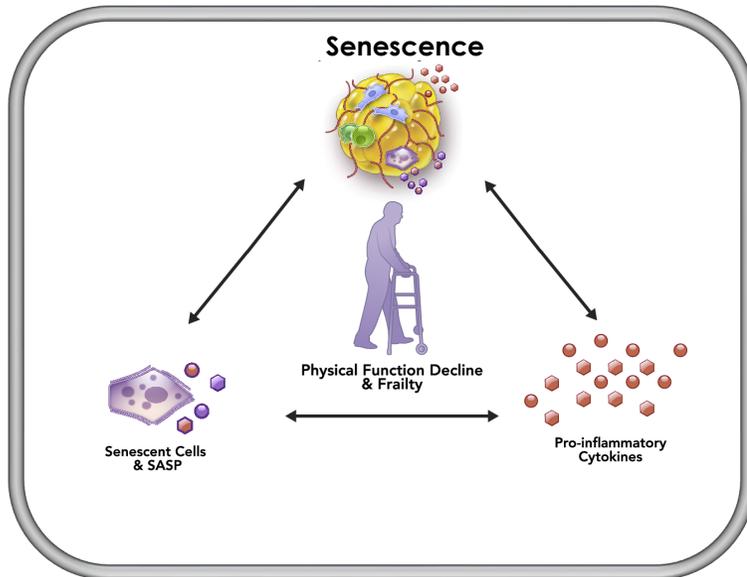


Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty

Michael B Stout ^{1, 2}, Jamie N Justice ³, Barbara J Nicklas ³, James L Kirkland ⁴

Older Recipients display Frailty Leading to Compromised Recipient Outcomes

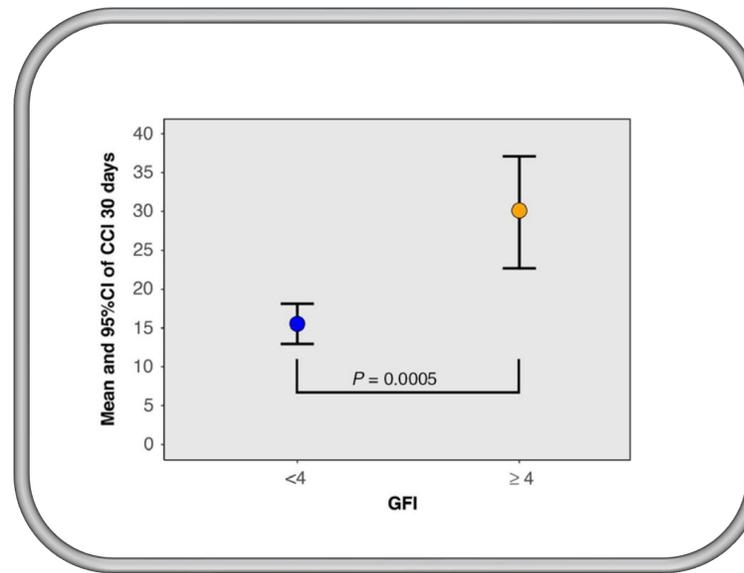
Cellular Senescence Induces Frailty



Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty

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Frailty Correlates with CCI 30

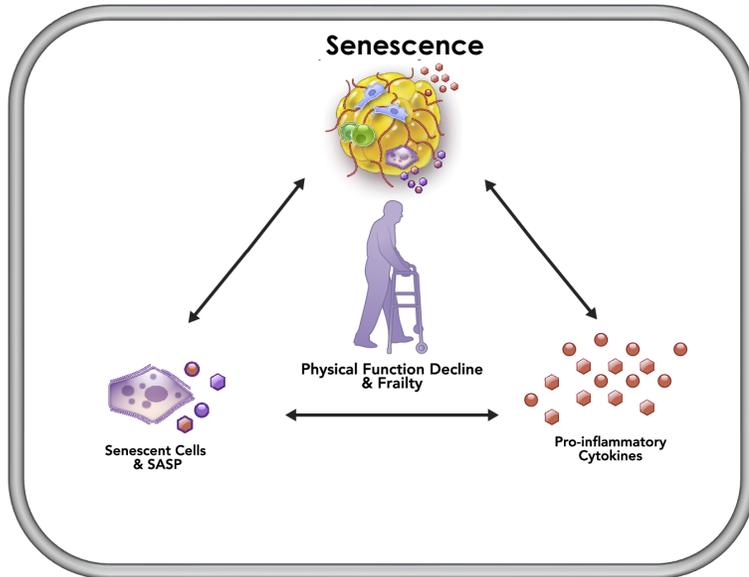


Frailty has a significant influence on postoperative complications after kidney transplantation—a prospective study on short-term outcomes

Lasse Schopmeyer¹, Mostafa El Mounni¹, Gertrude J Nieuwenhuijs-Moeke², Stefan P Berger³, Stephan J L Bakker³, Robert A Pol¹

Older Recipients display Frailty Leading to Compromised Recipient Outcomes

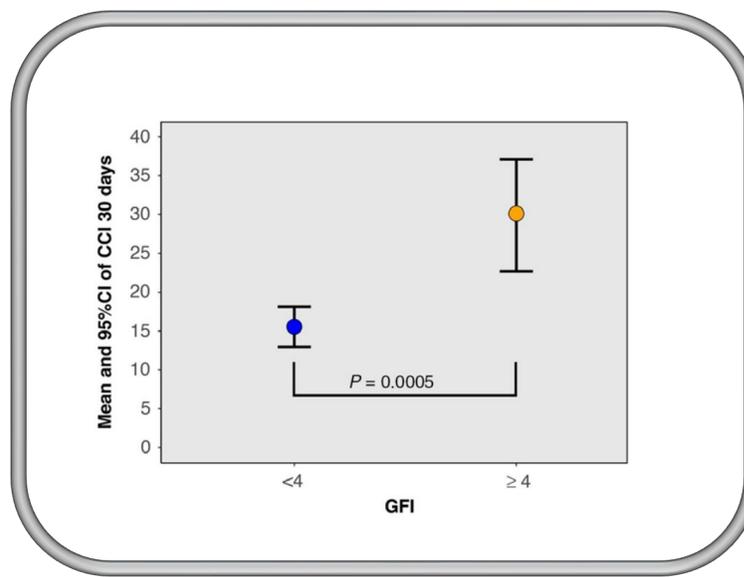
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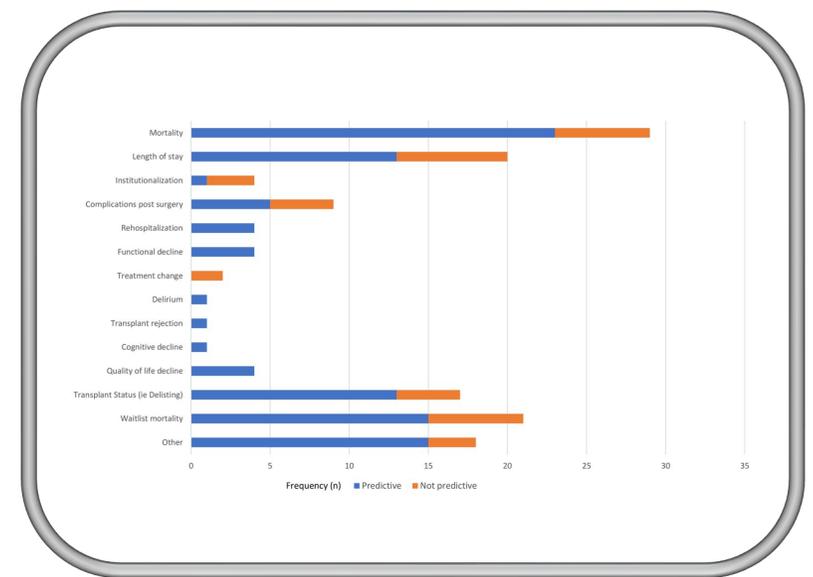
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Association: Frailty and Adverse Outcomes



Frailty and solid-organ transplant candidates: a scoping review

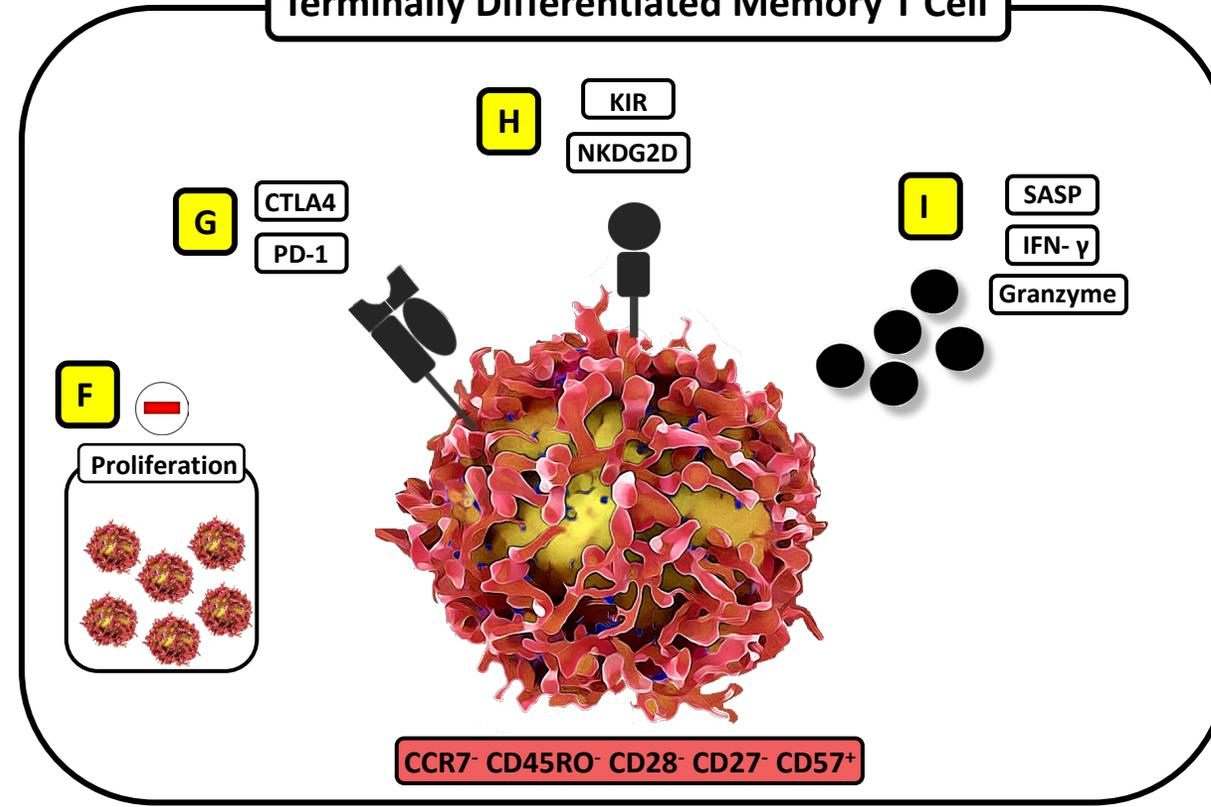
Jonathan Kao ^{1 2}, Natasha Reid ³, Ruth E Hubbard ^{4 3}, Ryan Homes ⁵, Leila Shafiee Hanjani ³, Ella Pearson ⁵, Benignus Logan ³, Shannon King ⁶, Sarah Fox ^{3 7}, Emily H Gordon ^{4 3}

Old Recipient

Transplantation



Terminally Differentiated Memory T Cell



Old Recipient

> [Front Immunol.](#) 2021 Jul 21;12:674016. doi: 10.3389/fimmu.2021.674016. eCollection 2021.

Allotransplantation Is Associated With Exacerbation of CD8 T-Cell Senescence: The Particular Place of the Innate CD8 T-Cell Component

Lauren Daniel^{1 2}, Marion Tassery³, Clara Lateur⁴, Antoine Thierry^{1 2 3}, André Herbelin^{1 2}, Jean-Marc Gombert^{1 2 4}, Alice Barbarin^{1 5}

> [Hum Immunol.](#) 2018 Sep;79(9):659-667. doi: 10.1016/j.humimm.2018.06.006. Epub 2018 Jun 15.

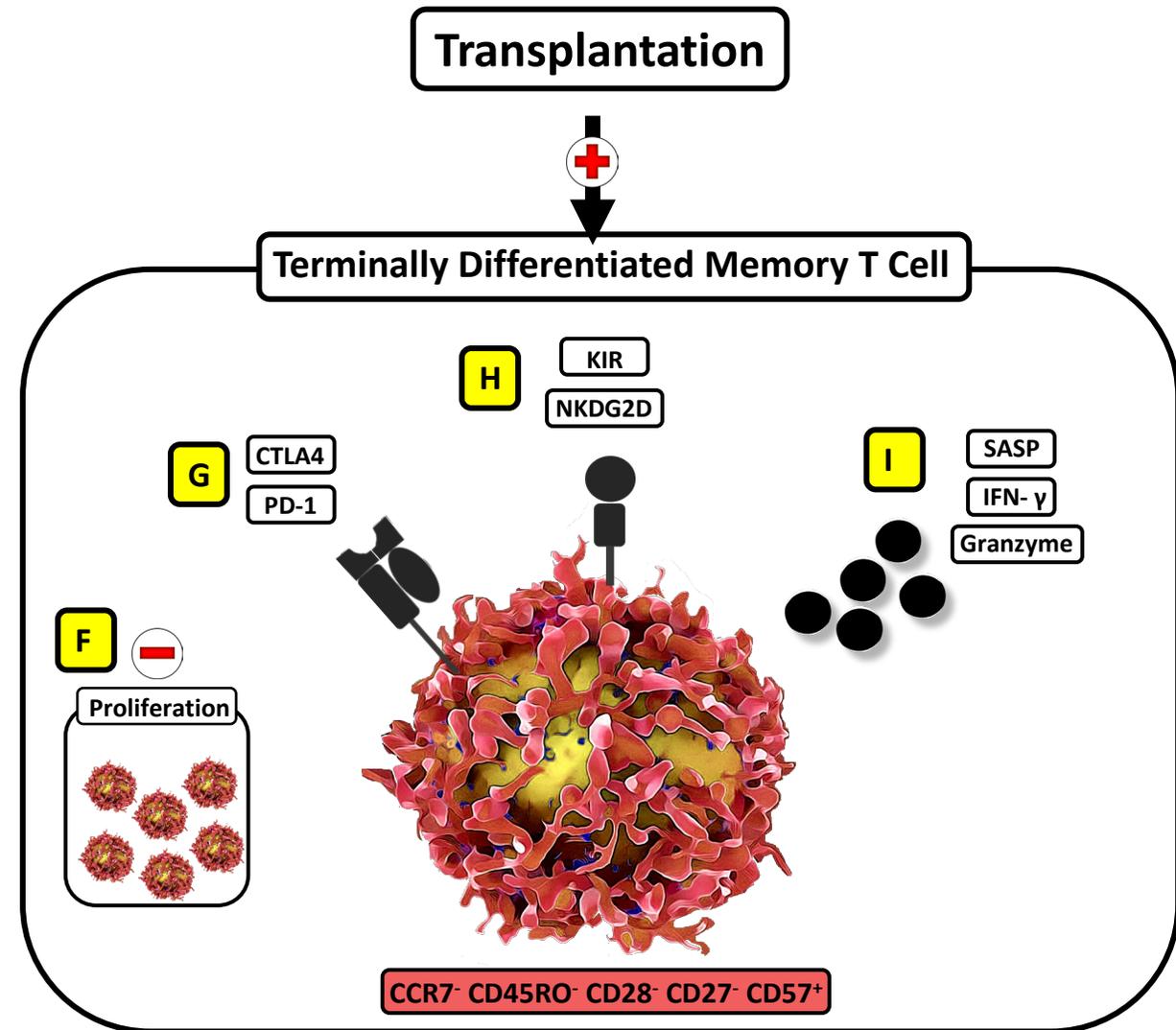
Increased T cell immunosenescence and accelerated maturation phenotypes in older kidney transplant recipients

J M Schaenman¹, M Rossetti², T Sidwell², V Groyberg², G Sunga², Y Korin², E Liang³, X Zhou⁴, B Abdalla⁵, E Lum⁵, S Bunnapradist⁵, T Pham⁵, G Danovitch⁵, E F Reed²

Multicenter Study > [Front Immunol.](#) 2021 May 27;12:661551. doi: 10.3389/fimmu.2021.661551. eCollection 2021.

Association of Premature Immune Aging and Cytomegalovirus After Solid Organ Transplant

Lauren E Higdon¹, Claire E Gustafson², Xuhuai Ji³, Malaya K Sahoo⁴, Benjamin A Pinsky^{4 5}, Kenneth B Margulies⁶, Holden T Maecker^{3 7}, Jorg Goronzy^{2 8}, Jonathan S Maltzman^{1 8}



Conclusions

1.

Older Transplant Recipients display a dysfunctional naive T cell compartment augmenting the susceptibility to infections

2.

Older Transplant Recipients display an altered T cell repertoire causing a distinct effects of common immunosuppressants

3.

Older Transplant Recipients display an increased number of senescent memory T cells accelerating aging

4.

Transplantation itself induces T cell Immunosenescence

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+ Max Emmert



Christine S. Falk, PhD



+ Jana Keil
+ Kerstin Beushausen

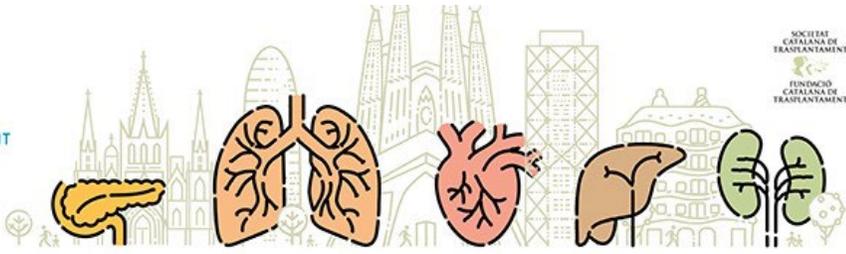


Fabio Ius, MD



+ Bettina Wiegmann





Gracias por tu atención!

Jasper Iske

Deutsches Herzzentrum der Charité

