DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2015

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Der Dr. Josef Steiner Krebsforschungspreis 2015
geht an Herrn Prof. Dr. Andrea Alimonti.

Herr Alimonti ist Leiter der Molekular - Onkologie am Institut für Onkologische Forschung in Bellinzona, Schweiz.
Die Preissumme beträgt gesamthaft CHF 1‘000‘000.

Dr. Josef Steiner Krebsforschungspreis 2015

Doktor Josef Steiner, Inhaber der „Dr. Steiner Apotheke und Bahnhofdrogerie“ in Biel, hat bei seinem Tode im Jahre 1983 ein grosses Vermögen hinterlassen, welches entsprechend seinem letzten Willen die finanzielle Basis der Dr. Josef Steiner Krebsstiftung bildete. Ziel der Stiftung ist die Förderung der Krebsforschung und die Auszeichnung hochverdienter Wissenschafter auf allen Gebieten der Krebsforschung. Als erster Preisträger konnte 1986 ein Schweizer, Dr. Peter Cerrutti, geehrt werden. Seither konnten zahlreiche hervorragende Wissenschafter aus Europa, USA, Australien und der Schweiz mit dem Dr. Josef Steiner Preis ausgezeichnet werden.

Im Bestreben, die Krebsforschung im Sinne des Stifters effizient und nachhaltig zu fördern, wird seit 1998 ein hervorragendes Forschungsprojekt für die Periode von vier Jahren mit einem Betrag von 1’000’000 Schweizerfranken unterstützt. Der Forschungsgruppenleiter oder die Forschungsgruppenleiterin wird zusätzlich mit einem persönlichen Preis in der Höhe von 50'000 Schweizerfranken ausgezeichnet.

Die Auswahl des preisgekrönten Projektes erfolgte nach einem mehrstufigen strengen Auswahlverfahren. Der Dr. Josef Steiner Preis 2015 wurde in renommierten Wissenschafts-zeitschriften ausgeschrieben. Die eingereichten Projektskizzen wurden vom Stiftungsrat und einer aus Fachvertretern zusammengesetzten Preiskommission gesichtet und bewertet. Als Kriterien wurden die wissenschaftliche Qualität und die Originalität der Projektskizzen, die Qualifikation der Projektverfasser, sowie die Beurteilung der Machbarkeit der vorgeschlagenen Projekte in Betracht gezogen. Fünf hervorragende Projektskizzen wurden ausgewählt und die Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für die Projekte wurden 2 vergleichende Beurteilungen von externen Gutachtern eingeholt.

Zusätzlich wurden die fünf Projektverfasser zu einem Symposium eingeladen, welches im Januar 2015 an der Universität Bern stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren ist Hr. Prof. Dr. Andrea Alimonti als Sieger hervorgegangen.

Laudatio für Herrn Prof. Dr. Andrea Alimonti

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis 2015 an Herrn Prof. Dr. Andrea Alimonti in Anerkennung seiner richtungsweisenden Forschungsergebnisse zur Immunkontrolle von Krebs und den daraus resultierenden neuen Therapiekonzepten. In eindrücklichen Arbeiten zeigte Prof. Dr. Alimonti, dass beim Prostatakarzinom bestimmte Immunzellen die Fähigkeit besitzen, Krebszellen zu ungehemmtem Wachstum anzuregen, anstatt diese in einen permanenten Wachstumsstillstand zu versetzen. Diese Erkenntnisse eröffnen Möglichkeiten neuartiger therapeutischer Ansätze gegen Krebs, die nachteilige Wechselwirkungen zwischen Immun- und Krebszellen gezielt blockieren.

Curriculum Vitae Andrea Alimonti

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Actual Position

2010 **Head, Molecular Oncology**
Institute of Oncology Research
Oncology Institute of Southern Switzerland
Bellinzona, Switzerland.

Education

2000 **MD degree, Magna Cum Laude (GPA: 110/110)**
University of Rome "*La Sapienza"* Rome, Italy

2004 **Residency in Clinical Oncology, Magna Cum Laude**
Regina Elena National Cancer Institute, Rome, Italy

2013 **PD, University of Lausanne (UNIL), Faculty of Biology and Medicine**
Lausanne, Switzerland

2013 **Professor Habilitation in Oncology and Molecular biology- Italian National Scientific Qualification (ANVUR 06/D3; 05/E2)**

2015 **Adjunct Professor, PhD program in Life Science, University of Padova, Italy**

Postdoctoral Training

2007– 2009 **BIDMC-Harvard Medical School** Boston, United States
Division of Cancer Genetics,
Lab.: Pier Paolo Pandolfi MD Phd.
Position: Postdoctoral Clinical/Research Fellow

2004–2007 **Memorial Sloan-Kettering Cancer Center**
New York, United States
Division of Human Pathology,
Lab.: Pier Paolo Pandolfi MD Phd.
Position: Postdoctoral Clinical/Research Fellow

2000–2004 **Regina Elena National Cancer Institute of Rome**
Rome, Italy
Division of Medical Oncology: Prof. Francesco Cognetti
Position: Resident in Clinical Oncology

Fellowships, Grants and Awards

2015 J. Steiner Cancer Research Award
2010 European Research Council (ERC) starting Grant
2011- 2014 Ambizione-SCORE grant (FNSNF)
2010- 2013 Swiss Bridge Award
2009-2010 European Society of Medical Oncology (ESMO) Award in Translational Research.
2008- 2012 Marie Curie International Reintegration Grant (IRG)
2004 - 2005 Susan Komen Breast Cancer Foundation (Komen Italia)
2003 - 2004 Italian Association of Clinical Oncology (AIOM)

Publiations (selection of 48 out of 65 papers)

1. Madhuri Kalathur, Alberto Toso, Jingjing Chen, Ajinkya Revandkar, Claudia Danzer-Baltzer, Ilaria Guccini, Abdullah Alajati, Manuela Sarti, Sandra Pinton, Lara Brambilla, Diletta Dimitri, Giuseppina Carbone, Ramon Garcia-Escudero, Alessandro Padova, Letizia Magnoni, Dr. Laura Maccari, Mr. Federico Malusa, Dr. Ravi Kiran Kalathur , Prof. Lorenzo Pinna, Maria Ruzzene, Giorgio Cozza, Carlo Catapano, Ian Frew & **Andrea Alimonti**. A chemogenomic screening identifies CK2 as a target for pro-senescence therapy in PTEN-deficient tumours. **Nat Commun. 2015** Jun 18;6:7227.
2. Diletta Di Mitri, Alberto Toso & **Andrea Alimonti**. Myeloid-derived -suppressor cells in prostate cancer therapy. **Clin Cancer Res 2015**, May 12.
3. Diletta Di Mitri, Alberto Toso & Andrea Alimonti. Tumour infiltrating myeloid cells drive senescence evasion and chemoresistance in cancer. **Oncoimmunology 2015** (accepted)
4. Alberto Toso, Diletta Di Mitri & Andrea Alimonti. Enhancing chemotherapy efficacy by reprogramming the senescence-associated secretory phenotype of prostate tumors. “A way to reactivate the anti-tumor immunity". **Oncoimmunology. 2015** Jan 22;4(3):e994380**.**
5. Abullah Alajati, Ilaria Guccini and Andrea Alimonti. Interaction of CDCP1 with HER2 enhances HER2-driven tumorigenesis and promotes trastuzumab resistance in breast cancer. **Cell Rep. 2015** Apr 15.
6. Diletta Di Mitri, Alberto Toso, Jing Jing Chen, Manuela Sarti, Sandra Pinton, Tanja Rezzonico Jost, Rocco D’Antuono, Erica Montani, Ramon Garcia-Escudero, Ilaria Guccini, Sabela Da Silva, Manuel Collado, Mario Eisenberger, Zhe Zheng, Carlo Catapano, Fabio Grassi & Andrea Alimonti. Tumour infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. **Nature 2014** Aug 24. doi: 10.1038/nature13638.
7. Alberto Toso, Ajinkya Revandkar, Diletta Di Mitri, Ilaria Guccini, Michele Proietti, Manuela Sarti, Sandra Pinton, Jiangwen Zhang, Madhuri Kalathur, Gianluca Civenni, David Jarrossay, Camilla Marini, Eugenio Scanziani, Fabio Grassi, Pier Paolo Pandolfi, Carlo V. Catapano and Andrea Alimonti. Enhancing chemotherapy efficacy in Pten-deficient prostate tumors by activating the senescence-associated antitumor immunity. **Cell Reports** 9, 1–15, October 9, 2014
8. Nardella C, Clohessy JG, **Alimonti A**, Panodlfi PP. Pro-senescence therapy for cancer treatment. **Nat Rev Cancer**. 2011 Jun 24;11(7):503-11
9. Carracedo A, **Alimonti A**, Pandolfi PP. PTEN level in tumor suppression: how much is too little? Cancer Res 2011 Feb 1;71(3):629-33
10. Nardella C, Lunardi A, Fedele G, Clohessy JG, **Alimonti A**, Kozma SC, Thomas G, Loda M, Pandolfi PP. Differential expression of S6K2 dictates tissue-specific requirement for S6K1 in mediating aberrant mTORC1 signaling and tumorigenesis. **Cancer Res.** 2011 May 15;71(10):3669-75
11. **A. Alimonti**, A. Carracedo, J. G. Clohessy, C. Nardella, L. C. Trotman, C. Nardella, A. Egia, L. Salmena, K. Sampieri, E. Brogi, J. Zhang, A. Richardson and P. P. Pandolfi. Subtle variations in Pten dose determine breast cancer susceptibility**. Nat Genet.** 2010 May;42(5):454-8.
12. **A. Alimonti**, C. Nardella, Z. Chen, J. G. Clohessy, L. C. Trotman, A. Carracedo, K. Cheng, S. Varmeh-Ziaie, M. B. Kastan, S.C. Kozma, G. Thomas, E. Rosivatz, R. Woscholski, F.Cognetti, H.I. Scher and P. P. Pandolfi. A novel type of cellular senescence that can be enhanced in mouse models and human tumor xenografts to suppress prostate tumorigenesis. **J Clin Invest.** 2010 Mar;120(3):681-93
13. **Alimonti A**. PTEN breast cancer susceptibility: a matter of dose Ecancermedicalscience. 010;4:192.
14. I. Pavese, F. Satta, P.Piergrossi, E. Brunetti & **A. Alimonti**. High serum levels of TNF-alpha and IL-6 predict the clinical outcome of treatment with human recombinant erythropoietin in anaemic cancer patients. **Ann Oncol**. 2009 Dec 23.
15. Chen Z, Carracedo A, Lin HK, Koutcher JA, Behrendt N, Egia A, **Alimonti A**, Carver BS, Gerald W, Teruya-Feldstein J, Loda M, Pandolfi PP. Differential p53-independent outcomes of p19(Arf) loss in oncogenesis **Sci Signal.** 2009 Aug 18;2(84):ra44.

16. Carver BS, Tran J, Gopalan A, Chen Z, Shaikh S, Carracedo A, **Alimonti A**, Nardella C, Varmeh S, Scardino PT, Cordon-Cardo C, Gerald W, Pandolfi PP. Aberrant ERG expression cooperates with loss of PTEN to promote cancer progression in the prostate. **Nat Genet.** 2009 May;41(5):619-24. Epub 2009 Apr 26.
17. Carver BS, Tran J, Chen Z, Carracedo-Perez A, **Alimonti A**, Nardella C, Gopalan A, Scardino PT, Cordon-Cardo C, Gerald W, Pandolfi PP. ETS rearrangements and prostate cancer initiation. **Nature.** 2009 Feb 12;457(7231):E1; discussion E2-3.
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19. Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, **Alimonti A**, Egia A, Sasaki AT, Thomas G, Kozma SC, Papa A, Nardella C, Cantley LC, Baselga J, Pandolfi PP. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. **J Clin Invest.** 2008 Sep;118(9):3065-74
20. Nardella C, Chen Z, Salmena L, Carracedo A, **Alimonti A**, Egia A, Carver B, Gerald W, Cordon-Cardo C, Pandolfi PP. Aberrant Rheb-mediated mTORC1 activation and Pten haploinsufficiency are cooperative oncogenic events. **Genes Dev**. 2008 Aug 15;22(16):2172-7
21. X. Wang, L. Trotman, T. Koppie, **A. Alimonti**, Z. Gao, J. Wang, H. Erdjument-Bromage, P. Tempst, C. Cordon-Cardo, P.P. Pandolfi and X. Jiang. NEDD 4-1 is the Proto-oncogenic Ubiquitin ligase for PTEN. **Cell.** 2007 Jan 12;128(1):129-39.
22. L.C. Trotman, X. Wang, **A. Alimonti**, Z. Chen, J. Teruya-Feldstein, S-G. Chi, H-J. Kim, H. Yang, N.P. Pavletich, B.S. Carver, H. Erdjument-Bromage, P. Tempst, C. Cordon-Cardo, T. Misteli. X. Jiang and P.P. Pandolfi. Ubiquitination regulates nuclear PTEN import and tumor suppression as revealed by inherited mutation**. Cell**. 2007 Jan 12; 128(1): 141-56.
23. L.C. Trotman, **A. Alimonti**, P.P. Scaglioni, J.A. Koutcher, C. Cordon-Cardo and P.P. Pandolfi. Identification of a tumour suppressor network opposing nuclear Akt function. **Nature,** 441:523-7 2006
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28. **Alimonti A**, Ferretti G, Cognetti F. Can the reliance of hormone receptor assays of surgical specimens be explained by the fluctuation of estrogen receptor, progesterone receptor, and HER-2 protein expression in tumor samples of premenopausal breast cancer patients? **J Clin Oncol**. 2005 Dec 1;23(34):8918
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32. Di Cosimo S, Ferretti G, Papaldo P, Carlini P, Fabi A, Ruggeri EM, **Alimonti A**, Nardoni C, Cognetti F. Does the concurrent use of anthracycline and granulocyte colony-stimulating factor influence the risk of secondary leukaemia in breast cancer women? **Ann Oncol.** 2005 Jul;16(7):1209-10. Epub 2005 Apr 27.
33. Migliore A, Tormenta S, Valente C, Massafra U, Martin Martin LS, Carmenini E, Bernardini A, **Alimonti A**. Intra-articular treatment with Hylan G-F 20 under ultrasound guidance in hip osteoarthritis. Clinical results after 12 months follow-up. Reumatismo. 2005 Jan-Mar;57(1):36-43.
34. **Andrea Alimonti**, Alain Gelibter, Ida Pavese, Francesco Satta, Gianluigi Ferretti, Francesco Cognetti, and Mario Di Palma. New approaches to prevent the intestinal toxicity of irinotecan-based regimens. **Cancer Treat Rev.** 2004 Oct; 30(6):555-62. Review.
35. **Alimonti A**, Di Cosimo S, Ferretti G, Sperduti I, Carlini P, Papaldo P, Fabi A, Gelibter A, Ciccarese M, Giannarelli D, Mandala M, Milella M, Ruggeri EM, Cognetti F. Incidence of chemotherapy-induced amenorrhea depending on the timing of treatment by menstrual cycle phase in women with early breast cancer. **Ann Oncol.** 2004 Jul;15(7):1065-71
36. Migliore A, Tormenta S, Martin LS, Valente C, Massafra U, Granata M, **Alimonti A**. Open pilot study of ultrasound-guided intra-articular injection of hylan G-F 20 (Synvisc) in the treatment of symptomatic hip osteoarthritis. Clin Rheumatol. 2005 Jun;24(3):285-9. Epub 2004 Dec 9.
37. Ferretti G, Di Cosimo S, Giannarelli D, Papaldo P, **Alimonti A**, et al. Endocrine adjuvant therapy and Her-2 neu over-expression: Can muddy water become clear ? **J Clin Oncol.** 2004 February
38. Migliore A, Tormenta S, Martin Martin LS, Valente C, Massafra U, Latini A, **Alimonti A**. Safety profile of 185 ultrasound-guided intra-articular injections for treatment of rheumatic diseases of the hip. Reumatismo. 2004 Apr-Jun;56(2):104-9.
39. **Alimonti A**, Di Cosimo S, Di Palma M, Ferretti G, Vecchione A. Is video-assisted thoracic surgery always safe? Minerva Chir. 2004 Aug;59(4):413-4
40. **Alimonti A**. et al. May colorectal cancer patients with Thymidylate-Sintetase positive liver metastases have an overall survival advantage by hepatyc arterial infusion alone? **J Clin Oncol.** 2003 Sep 15;21(18):3543-4
41. **Alimonti A**. et al "A woman with subacute motor weakness and left renal mass". **Am J Med**. 2003 Jun 1;114(8):706-8
42. **Alimonti A.** et al. A man with a deltoid mass and erythrocytosis: case report and review of the cases. Anticancer Res. 2003 Nov-Dec; 23(6D):5181-4.
43. Martin-Martin LS, Latini A, Pagano A, Ragno A, Stasi R, Coppe A, Davoli G, Crescenzi A, **Alimonti A**, Migliore A. A new mathematical model based on clinical and laboratory variables for the diagnosis of Sjogren's syndrome. Clin Rheumatol. 2003 May;22(2):123-124
44. **Alimonti A** et al. Prevention of irinotecan plus 5-fluorouracil/leucovorin-induced diarrhoea by oral administration of neomycin plus bacitracin in first-line treatment of advanced colorectal cancer**.** **Ann. Oncol** 2003 14: 805-a-806-a
45. Migliore A, Martin LS, **Alimonti A**, Valente C, Tormenta S. Efficacy and safety of viscosupplementation by ultrasound-guided intra-articular injection in osteoarthritis of the hip. Osteoarthritis Cartilage. 2003 Apr;11(4):305-6
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Dr. Andrea Alimonti beschreibt seine preisgekröntes Projekt wie folgt:

Cellular senescence is a stable cell growth arrest that is normally observed in all the cells of human tissues during aging. Recently, we and others have discovered that senescence can also occur in tumor cells, thereby limiting tumor cell proliferation. Different stimuli can induce senescence in cancer cells. Loss of some tumor suppressor genes or overexpression of some oncogenes can promote senescence in tumor cells blocking tumorigenesis. Chemotherapy, radiotherapy and targeted therapies can also promote senescence in tumors. Therefore senescence is a barrier that opposes tumor development. Few years ago, we have demonstrated that targeted compounds that enhance senescence in cancer can be used for cancer therapy with minimal toxicity for normal cells. We have named this novel therapeutic approach “pro-senescence” therapy for cancer. During the years our research has focused on the identification of novel compounds that enhance senescence in cancer and on the characterization of the mechanisms by which tumor cells evade senescence driven by chemo or targeted therapy.

Recent findings have established a novel link between senescence and the tumor immune response in cancer. Immune cells such as macrophages or natural killer cells can promote the clearance of senescent tumor cells thereby contributing to the tumor suppressive function of senescence in cancer. TH1 lymphocytes can induce senescence and tumor inhibition in pancreatic cancers by secreting different cytokines in the tumor microenvironment. In contrast we have demonstrated, that tumor-infiltrating $GR1^+$ myeloid cells can antagonize senescence driven by *Pten* loss and chemotherapy-induced senescence in a model of prostate cancer. Interestingly we have also shown that compounds that block the recruitment of myeloid cells in tumors can enhance the efficacy of chemotherapy-induced senescence. Therefore different tumor infiltrating immune subsets can behave as positive or negative regulators of senescence in cancer, contributing to tumor inhibition or proliferation. These findings have paved the way for the development of treatments that combine different immunotherapies with pro-senescence compounds in order to promote the activation of a “positive” tumor immune response. Main objective of this proposal is to identify novel treatment modalities that reprogram the tumor immune response to enhance the efficacy of “pro-senescence” therapy for cancer. We believe that such approach may increase the efficacy of already available chemotherapy or of novel pro-senescence compounds.

Intriguingly, we have recently found that tumor associated macrophages (TAMs) can promote senescence in cancer. TAMs exist as a phenotypic spectrum ranging from tumoricidal M1 to tumor promoting M2. We have collected evidence that a novel compound that interferes with the M1-M2 macrophage polarization also activates senescence and tumor clearance in advanced prostate tumors by increasing the numbers of intratumoral M1. We have found that M1 macrophages can induce senescence in tumor cells by secreting in the tumor microenvironment several pro-senescence cytokines. Therefore treatments that block the polarization of macrophages in M2 should enhance senescence in cancer and could be used for pro-senescence therapy when used alone or in combination with chemo or targeted therapies (Figure1).

An additional objective of this proposal is to characterize whether secreted factors released by senescent tumor cells subjected to chemotherapy, can promote evasion of the tumor immune response. We have found that some cytokines released by senescent cells can mediate paracrine transmission of senescence to lymphocytes in different tumor models. As previously demonstrated, senescent lymphocytes are unable to proliferate and promote an active tumor immune response. Therefore, we will also assess whether neutralizing antibodies that

antagonize secreted factors released by senescent cells can be used to potentiate the activity of T-cells in cancer thereby sustaining tumor immune clearance. In other experiments we will assess whether available treatments that interfere the secretome of the tumor cells can maintain younger T lymphocytes sustaining tumor clearance during chemotherapy (Figure 1). Finally we will assess *in vivo* whether combination of pro-senescence compounds with immunomodulators are effective in restricting prostate cancer progression in tumors at advance stage of disease. Our final objective is to translate to the clinic, these findings. This will be achieved by testing these compounds in prostate cancer in proof of concept trials that will open the way to larger clinical trials. We are convinced that this proposal will generate a series of findings that will impact on the therapy and prognosis of patients affected by prostate cancer. This tumor still remains the second cause of death for cancer in men both in Switzerland and in the Western World. Therefore novel treatments that prolong the prognosis of prostate cancer patients may have a tremendous social impact.

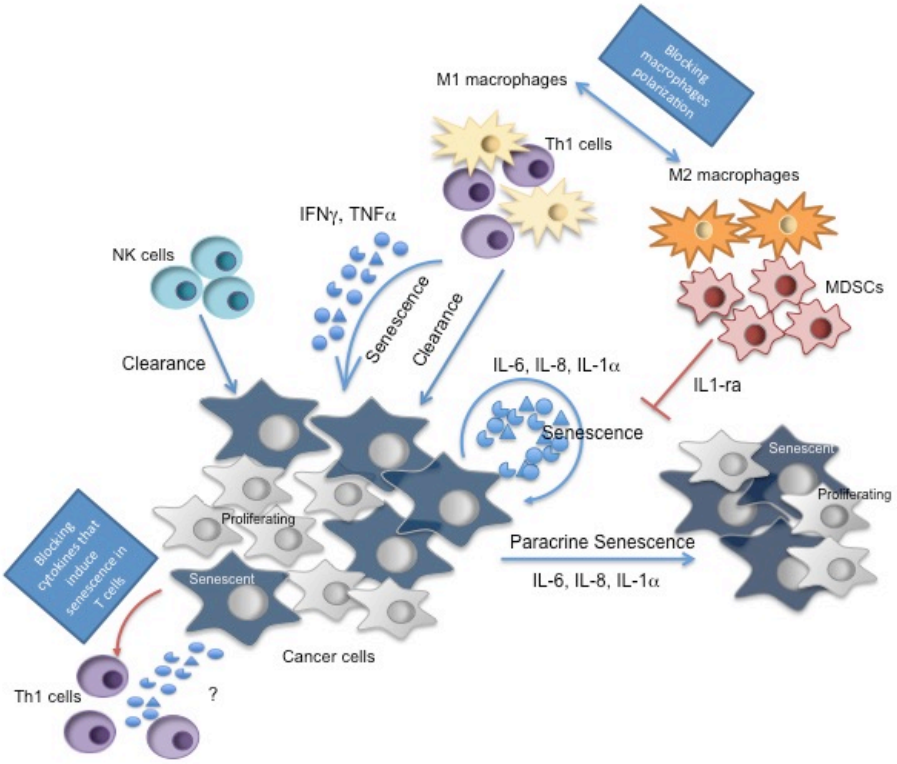

Figure 1. Positive and negative interactions between senescence in tumors and the tumor immune response. Blue arrows indicate positive interactions between the tumor immune response and senescent tumor cells. Red arrows indicate negative interactions. Blue squares indicate potential entry points to enhance the efficacy of pro-senescence therapy.