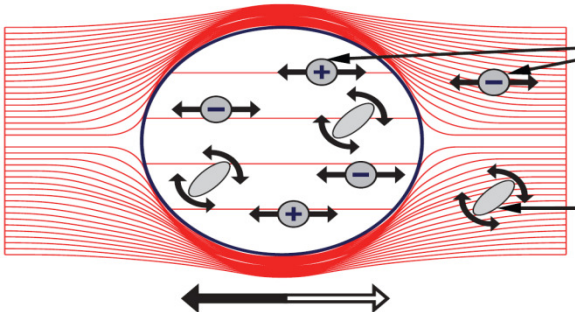
Tumor Treating Fields (TTFields) induced cancer cell death may be immunogenic resulting in enhanced antitumor efficacy when combined with immune-modulating therapy

Moshe Giladi
Head of Preclinical Studies
Novocure Ltd.

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TTFields Distribution in and Around Quiescent and Dividing Cells

A



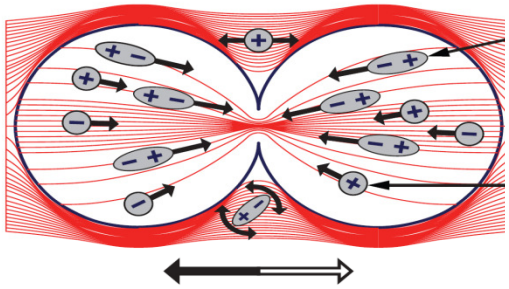
Oscillating direction of force acting on charge

Oscillating direction of force acting on dipole

Field of alternating direction

uniform electric field leading to dipoles alignment

B



Unidirectional net force acting on dipole during all cycle phases

Unidirectional net force acting on charge during all cycle phases

Field of alternating direction

nonuniform electric field leading to dielectrophoresis

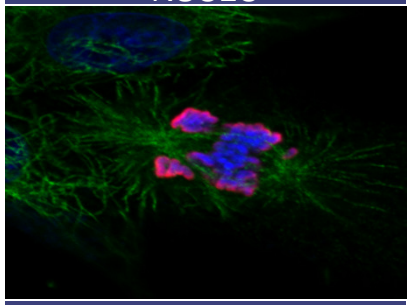
Kirson ED, Dbalý V, Tovarys F, et al. *PNAS*. 2007;104(24):10151-10157.

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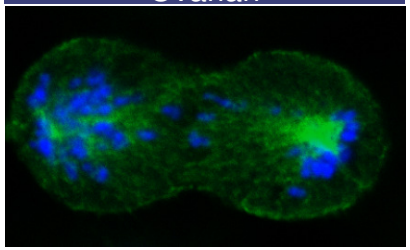
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TTFields MOA Summary

NSCLC

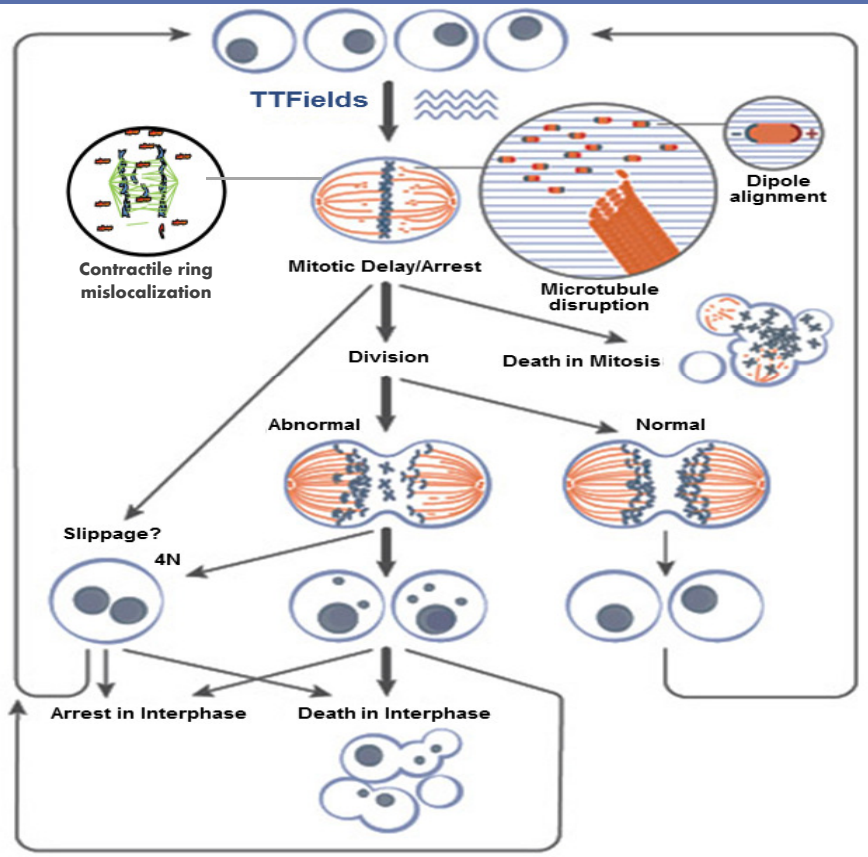


Ovarian

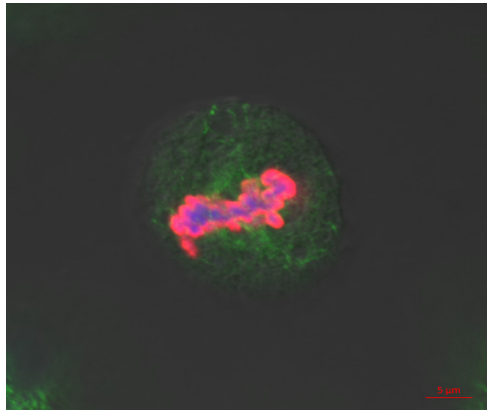


Glioma



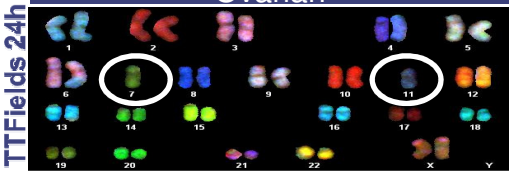


NSCLC

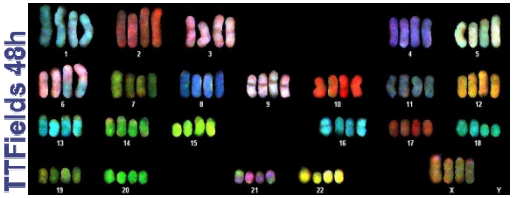


Ovarian

TTFields 24h



TTFields 48h



Modified from Giladi M, Schneiderman RS, *Scientific Reports,* 2015 and Gera et al., PLoS One. 2015

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TTFields Are Delivered by Optune

- Single-use transducer arrays deliver TTFields through the scalp[1]
  - Arrays deliver TTFields at a low intensity (1-3 V/cm) and intermediate frequency (200 kHz)[2]



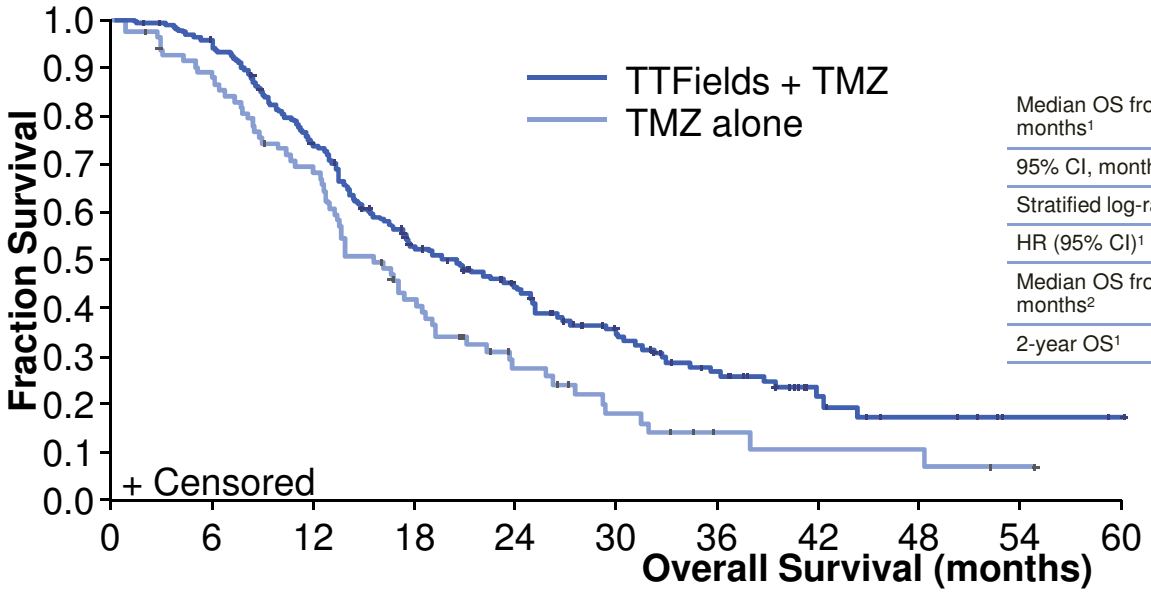


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1. Optune Patient Information and Operation Manual. Novocure Inc. Document number QSD-QR-331. November 1, 2014. **2**. Optune Instructions for Use. Novocure Inc. Document number QSD-QR-330. November 2014.

EF-14: Secondary Endpoint, OS[1]
Interim Analysis, Per Protocol Population



	TTFields + TMZ (n=196)	TMZ Alone (n=84)
Median OS from randomization, months[1]	**20.5**	**15.6**
95% CI, months[1]	**16.6-24.9**	**12.9-18.5**
Stratified log-rank[1]	***P*=0.0042**	
HR (95% CI)[1]	**0.666 (0.495-0.898)**	
Median OS from diagnosis, months[2]	**24.4**	**19.4**
2-year OS[1]	**48%**	**32%**

- In the final analysis (n=609), TTFields + TMZ extended median OS by 4.4 months, consistent with the interim analysis (n=280)[1]

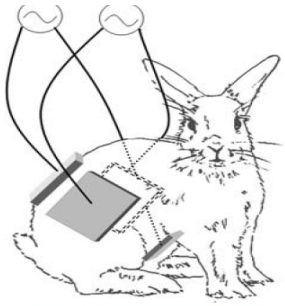
TMZ, temozolomide; CI, confidence interval; HR, hazard ratio; OS, overall survival.

References: **1.** Optune Instructions for Use. Novocure. Document number QSD-QR-330. 2015. **2.** Novocure Data on File OPT-103.

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In Vivo Evidence of Immune Stimulation in Response to TTFields Application



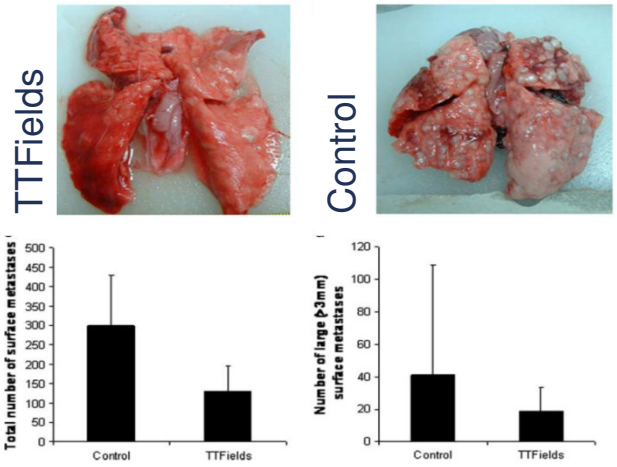
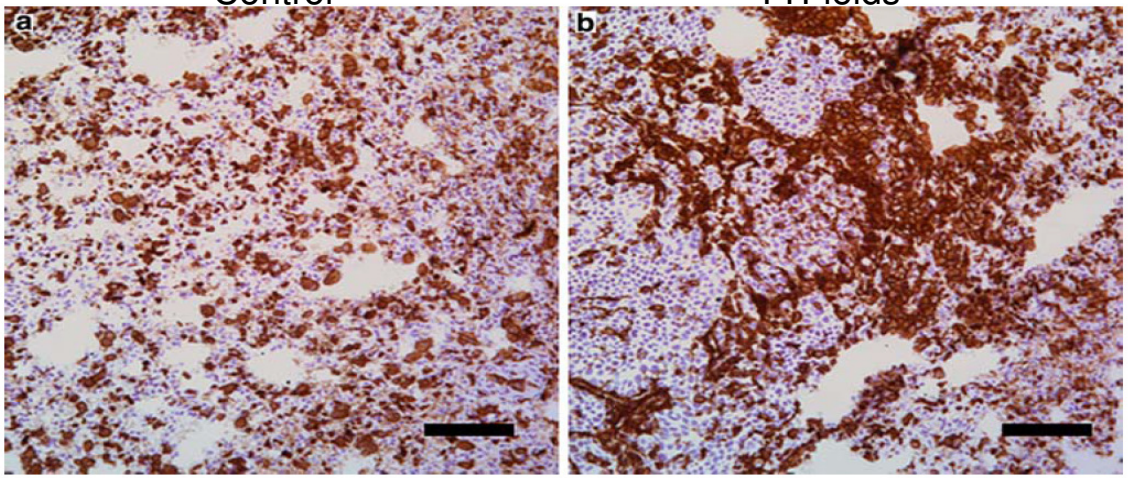


Table 1 Lymphocyte infiltration in lung tumors as revealed by immuno-histochemical staining

Treatment	CD4	CD8	CD45	CD19
Control	2.0 ± 0.8	0.8 ± 0.5	2.0 ± 0.8	0
TTFields	3.4 ± 0.9	1.6 ± 0.5	3.6 ± 0.5	0

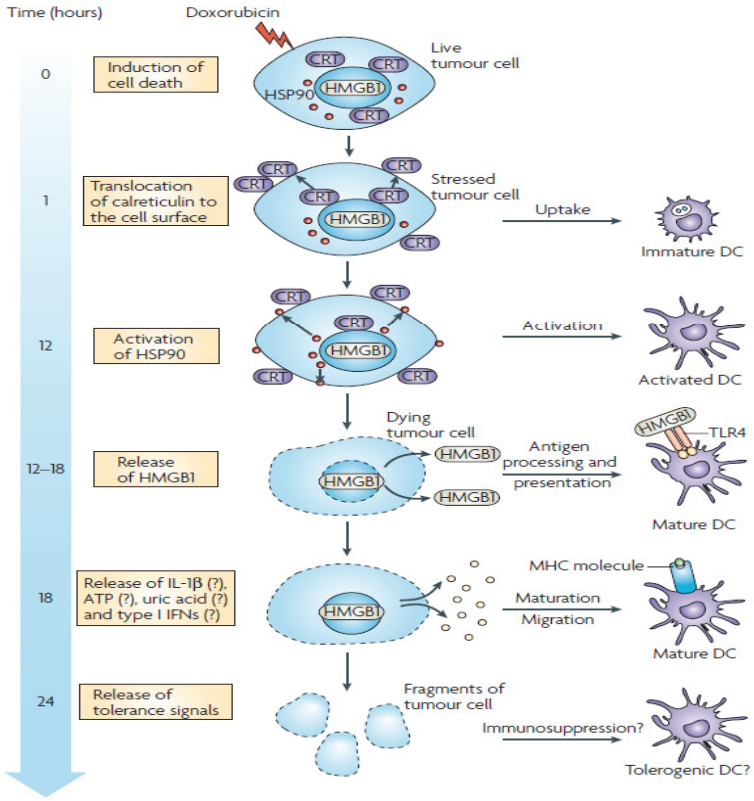
Control TTFields



Kirson ED, Giladi M, Gurvich Z.et al. Clin Exp Met. 2009;26:633-640.

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Immunogenic Cell Death - Sequential Events that Link Tumor-Cell Stress with Activation of Antigen-Presenting Cells



Calreticulin acts on the scavenger receptor (Eat me signal)

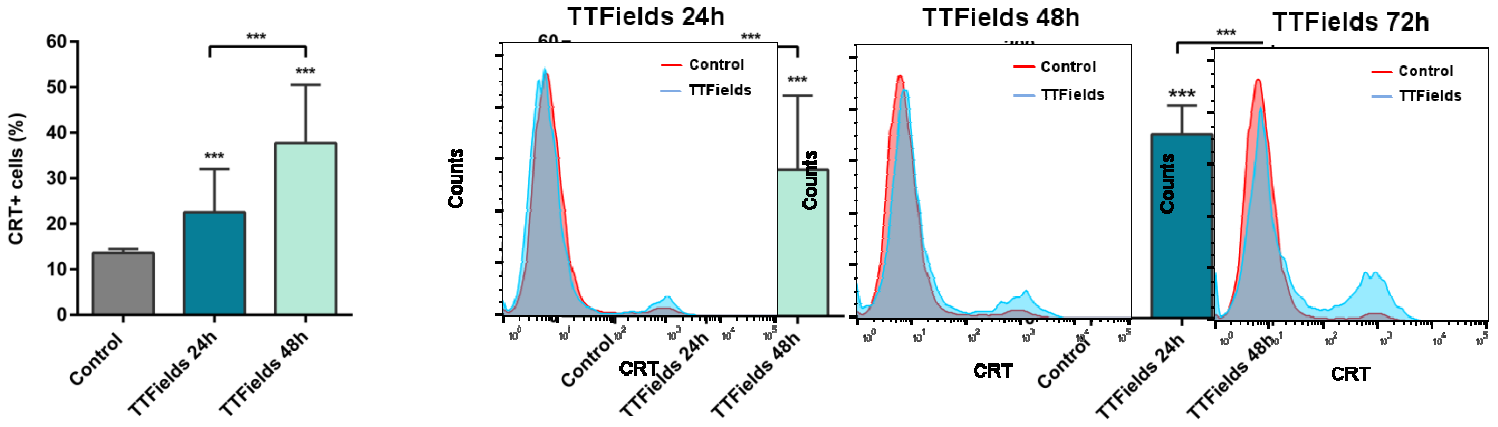
Toll-like receptor 4 is responsible for activating the innate immune system.

Zitvogel et.al , Nature reviews Immunology 2008

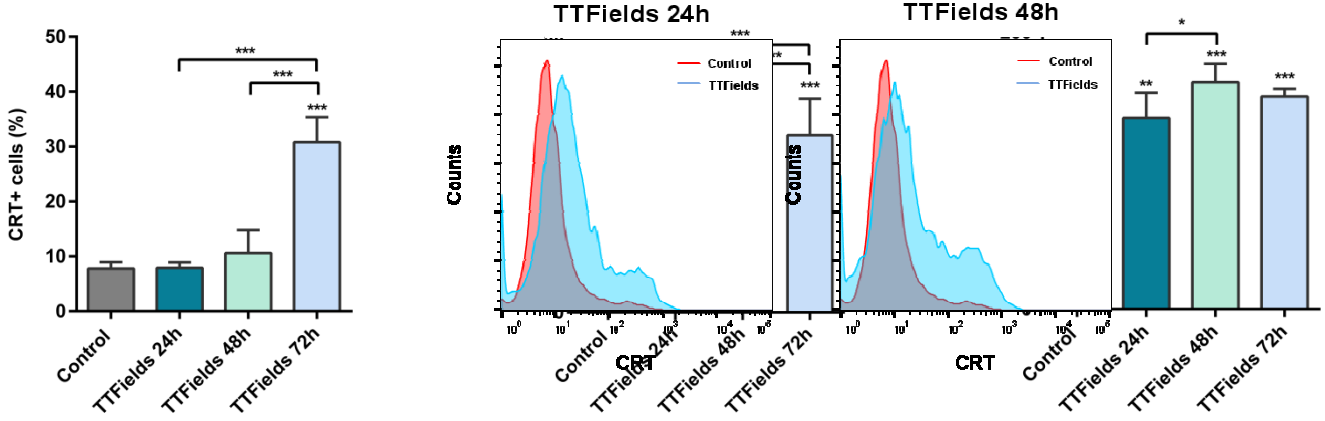
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TTFields Application Mediate Cell Surface Exposure of Calreticulin

LLC-1
Mouse lung cancer



MOSE-L
Mouse ovarian cancer

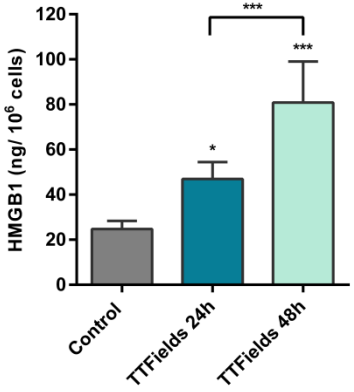


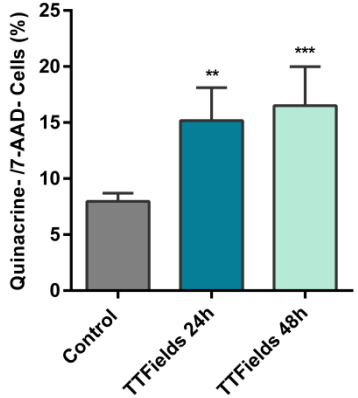
Giladi et al., AAI 2016

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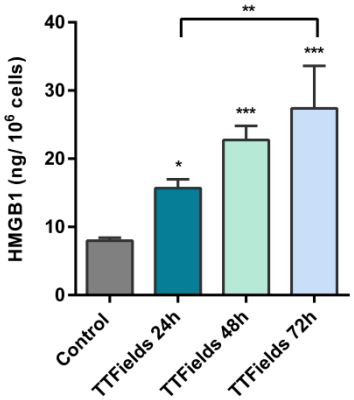
TTFields Induce an Increase in HMGB1 Release and a Reduction in Intracellular ATP Levels

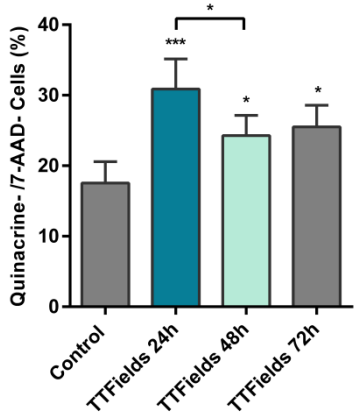
LLC-1
Mouse lung cancer





MOSE-L
Mouse ovarian cancer





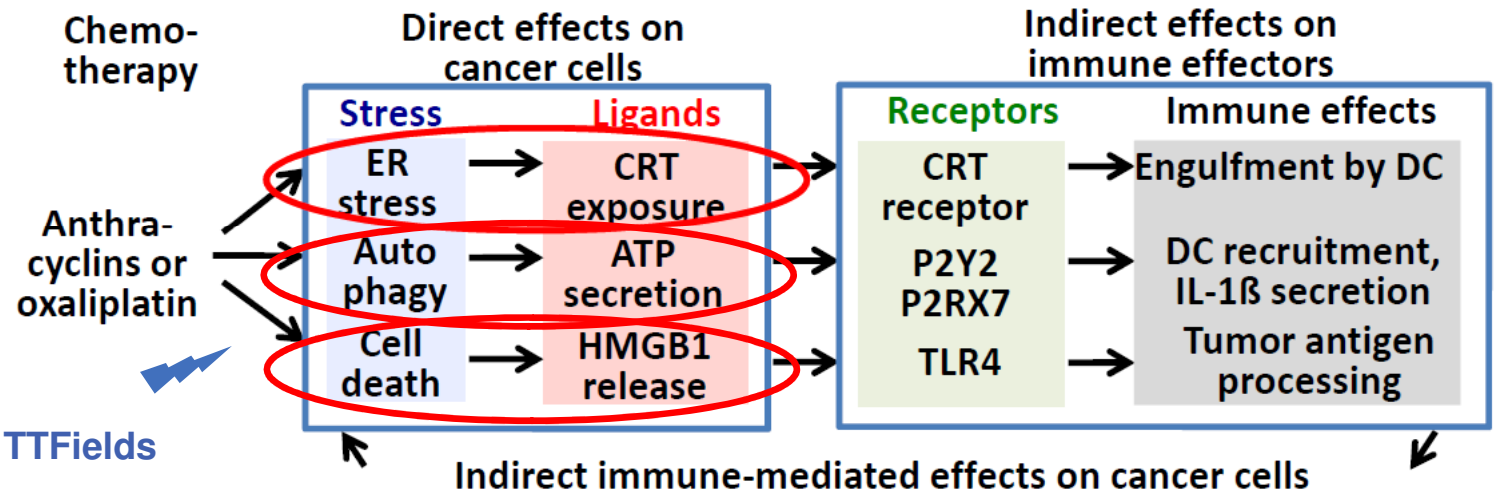
Giladi et al., AAI 2016

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Sequential Events that Link Tumor-Cell Stress with Activation of Antigen-Presenting Cells

Immunogenic cell death: the rules



Obeid et al. 2007 Nat Med
Apetoh et al. 2007 Nat Med
Ghiringhelli et al. 2009 Nat Med
Michaud et al. 2011 Science
Menger et al. 2012 Science Transl Med

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Cancer Immunity Cycle

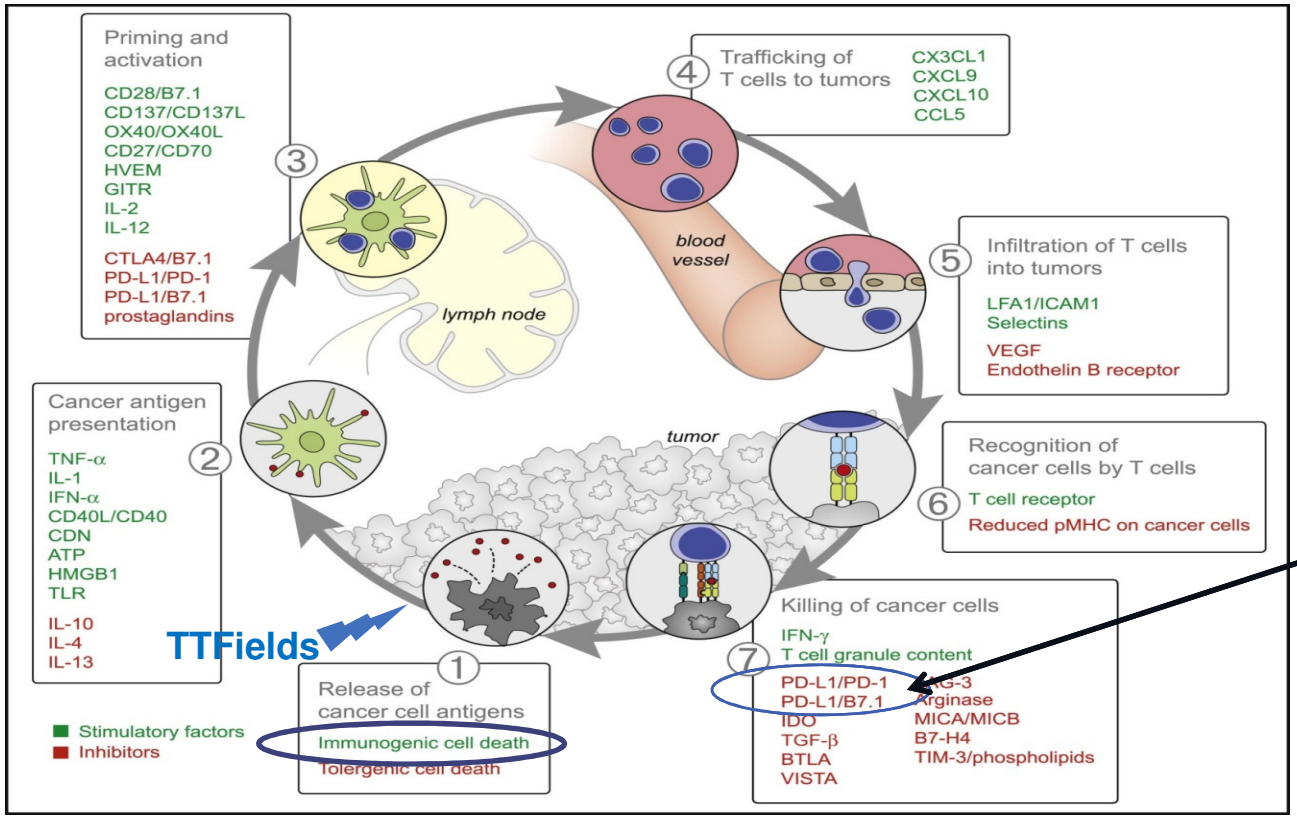


Image from *Chen DS, et al. Immunity. 39:1-10*. Copyright © 2013 Elsevier Inc.

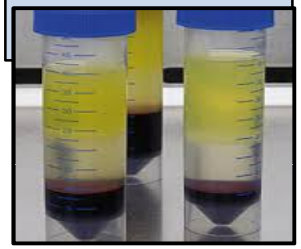
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Assay design

Leukocyte fraction of blood donation acquired from MADA: ample supply of cells from multiple donors (5)



PBMC production &



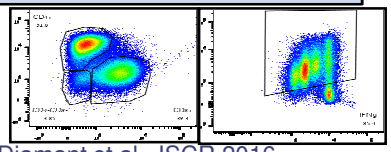
- CFSE staining to detect proliferation
- Activate cells with PHA Superantigen

Incubate in normal conditions / *inovitro* for 3.5 days



Stain to:
- Isolate T-cells
- Detect immune activity:
  - ✓ Cytokine Secretion
  - ✓ Cytotoxic Degranulation
  - ✓ Activation/ Exhaustion Marker

Flow cytometry analysis

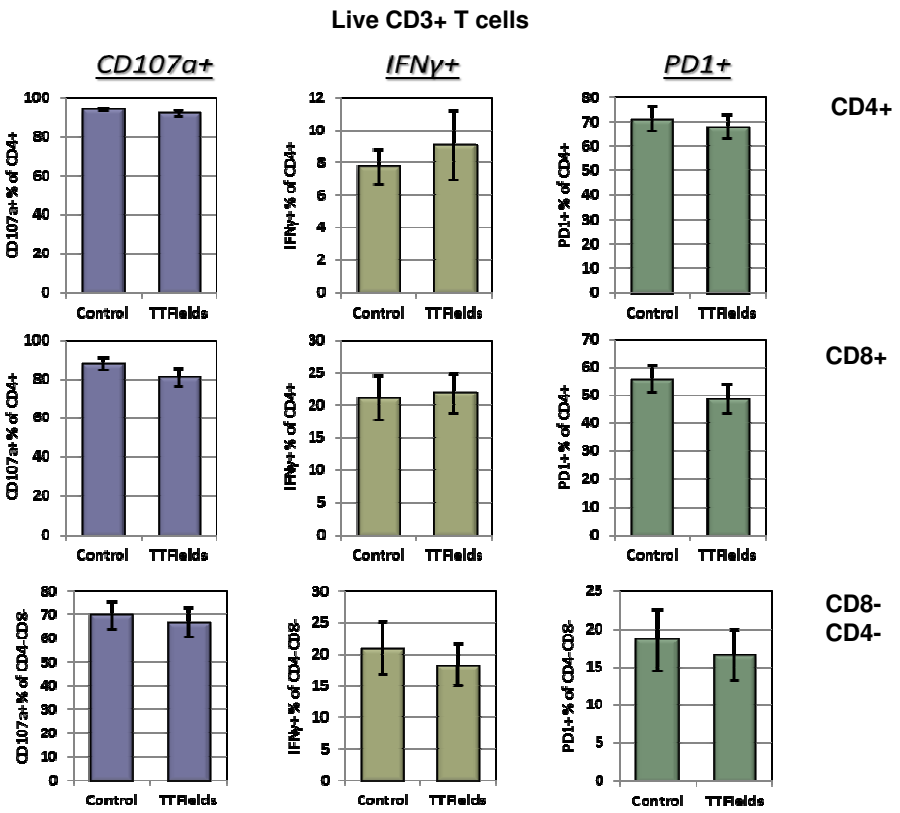


Diamant et al., ISCR 2016

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Effect of TTFields on T-cell activation in PBMC culture

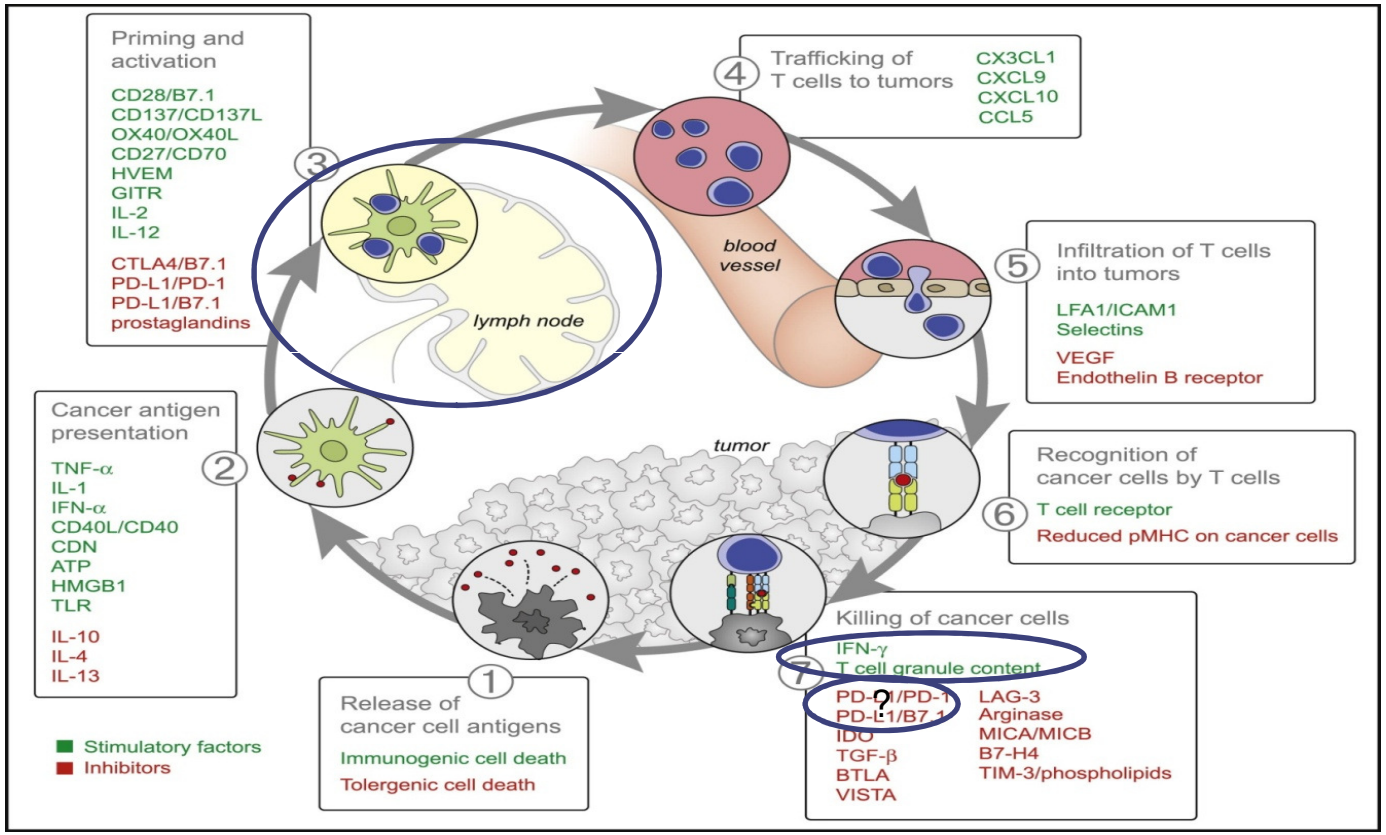
- Results indicate activated T cells treated with TTFields **exhibit slight /no decrease** (sometimes even increase) in IFNγ secretion, PD1 up-regulation, and cD107a surface presentation**.**



Diamant et al., ISCR 2016

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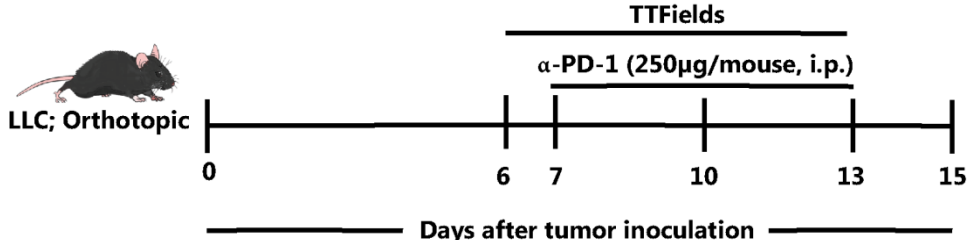
Cancer Immunity Cycle

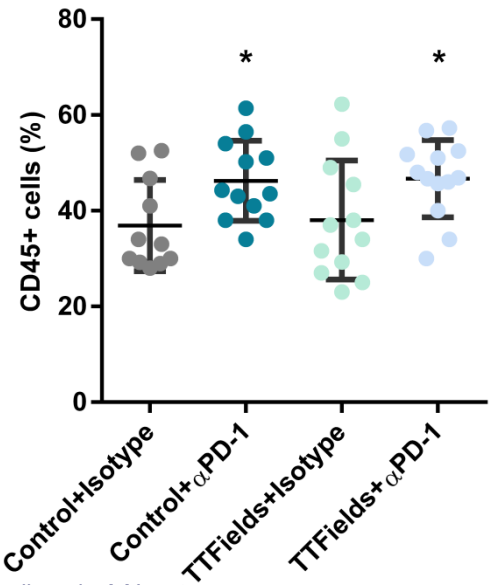


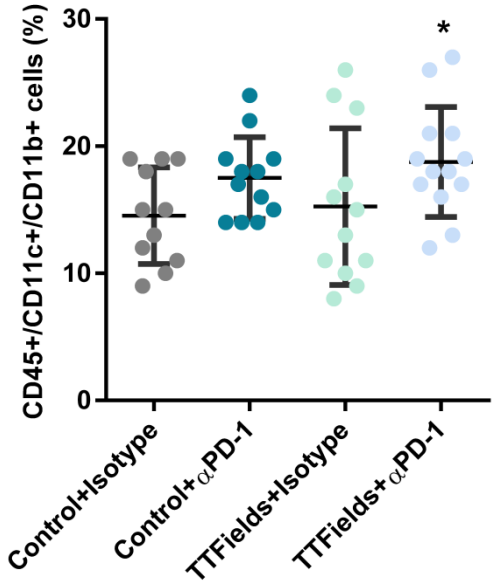
Chen DS, et al. Immunity. 39:1-10, 2013.

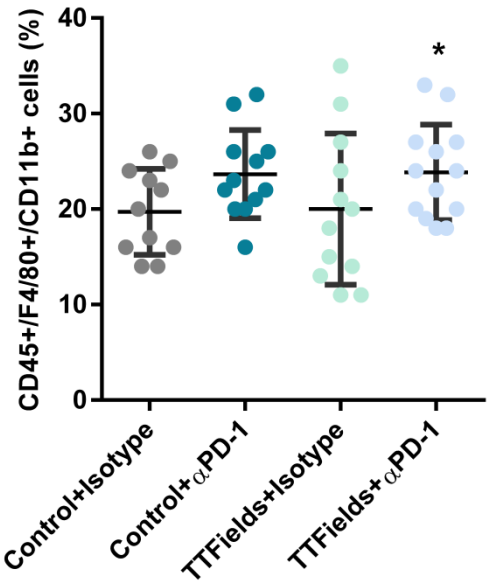
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TTFields in Combination with Anti-PD-1 Lead to an Increase in Antigen Presenting Cells Infiltration to the Tumor





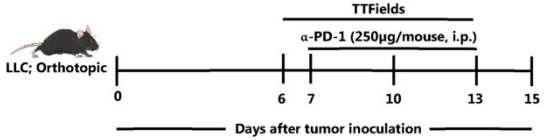


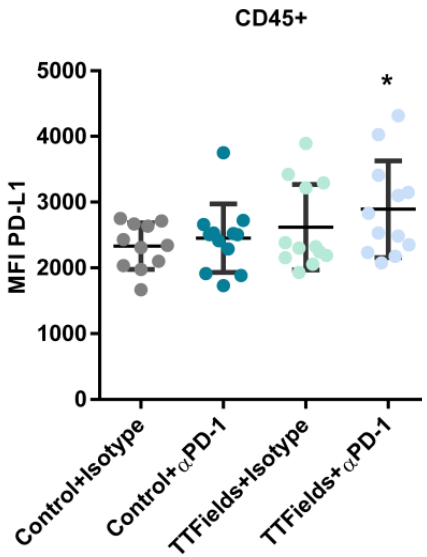


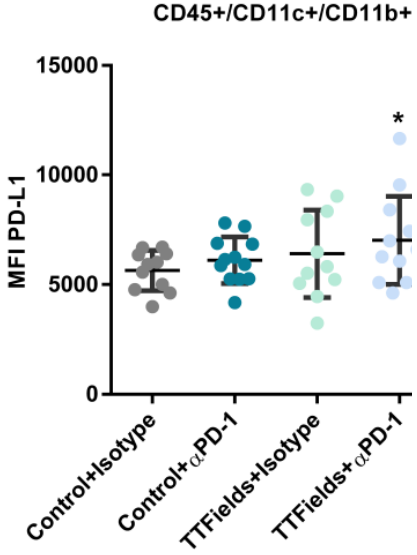
Giladi et al., AAI 2016

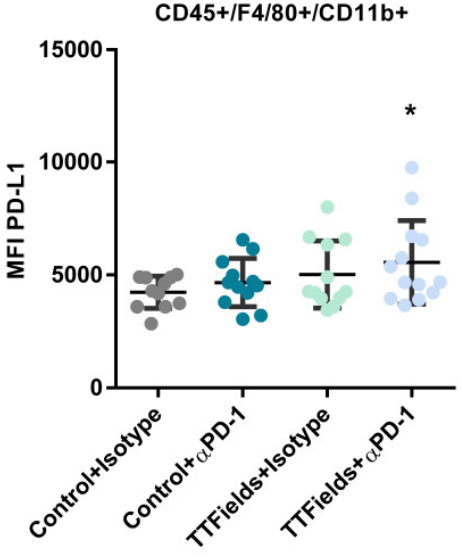
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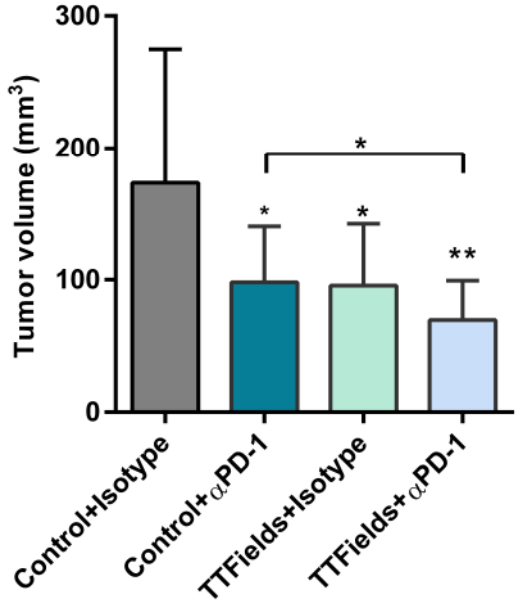
TTFields in Combination with Anti-PD-1 Lead to Elevated PD-L1 Expression and Reduced Tumor Volume











Giladi et al., AAI 2016

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Summary of TTFields effects

- Disrupt normal mitotic spindle assembly leading to mitotic catastrophe
- Lead to abnormal chromosomal segregation
- Induce autophagy
- Activate immunogenic cell death
- Demonstrate enhanced antitumor efficacy when combined with immune-modulating therapy

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Cancer Immunity Cycle

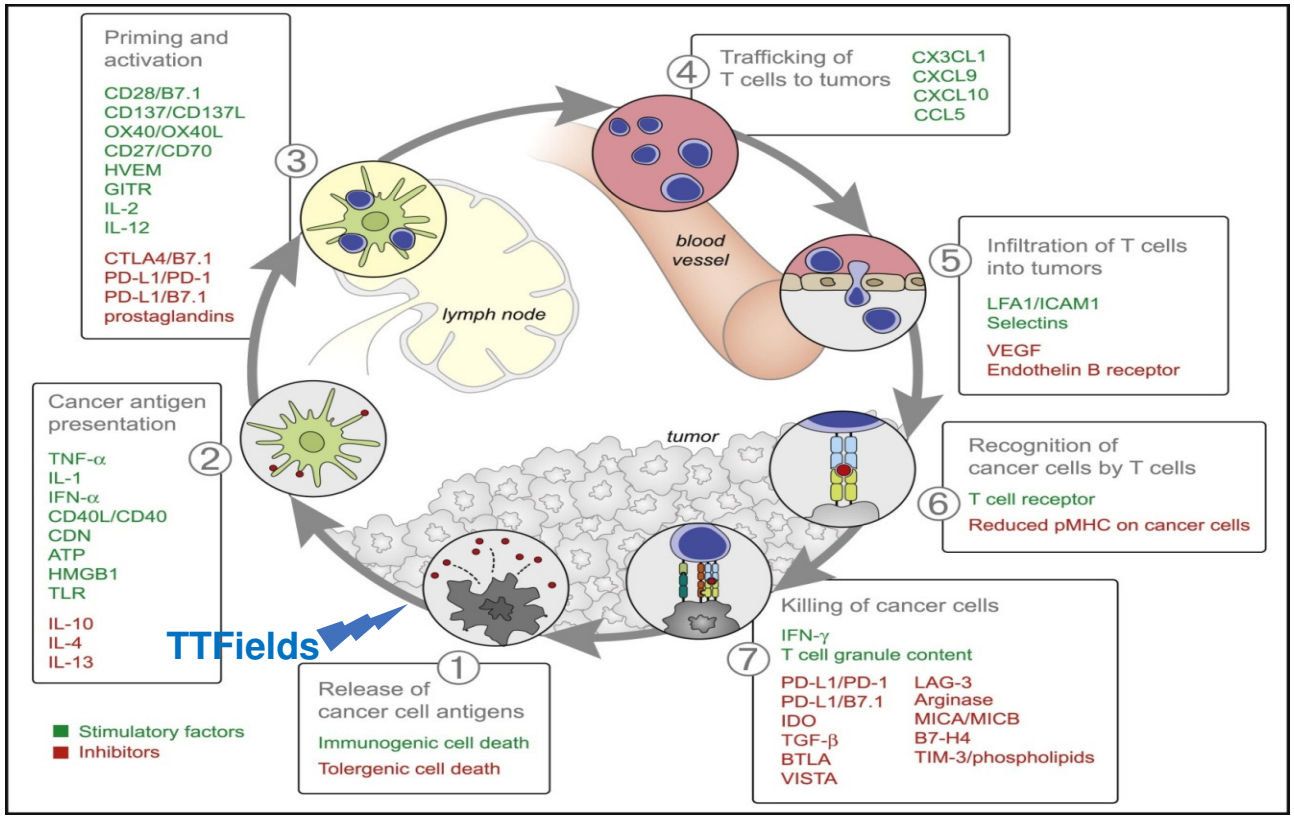


Image from *Chen DS, et al. Immunity. 39:1-10*. Copyright © 2013 Elsevier Inc.

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Novocure preclinical studies












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