Sviluppo di vaccini terapeutici mediante l'uso di cellule dendritiche e citochine

Filippo Belardelli

"Le nuove sfide della ricerca oncologica: verso una partnership tra Enti Pubblici e Industria nella regione Lazio"

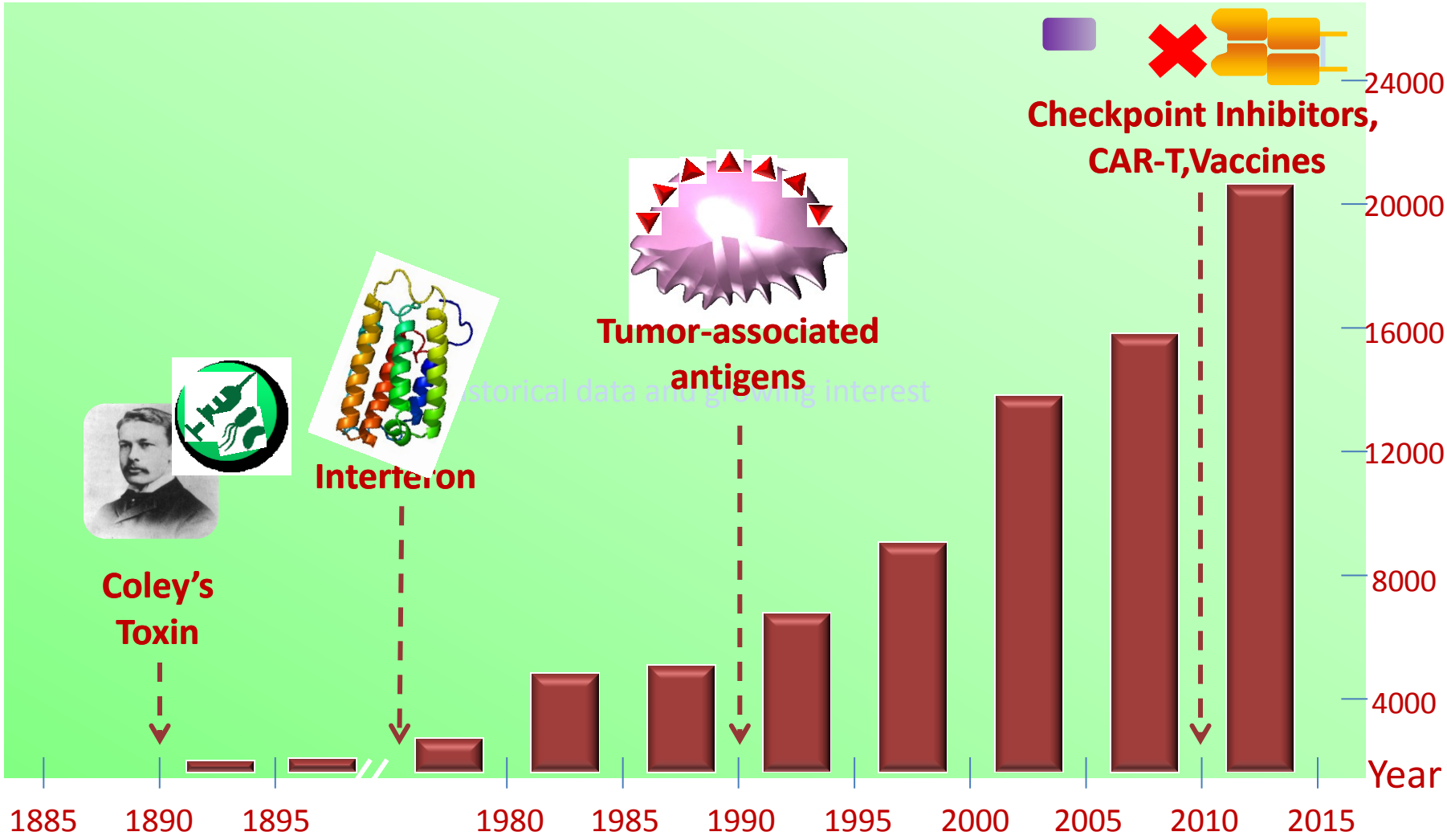
Roma, 17 maggio 2017

REGIONE LAZIO

ISTITUTO SUPERIORE DI SANITÀ

LAZIO INNOVA

La storia alterna dell'immunoterapia dei tumori ed il momento magico di oggi



Cancer Immunotherapy

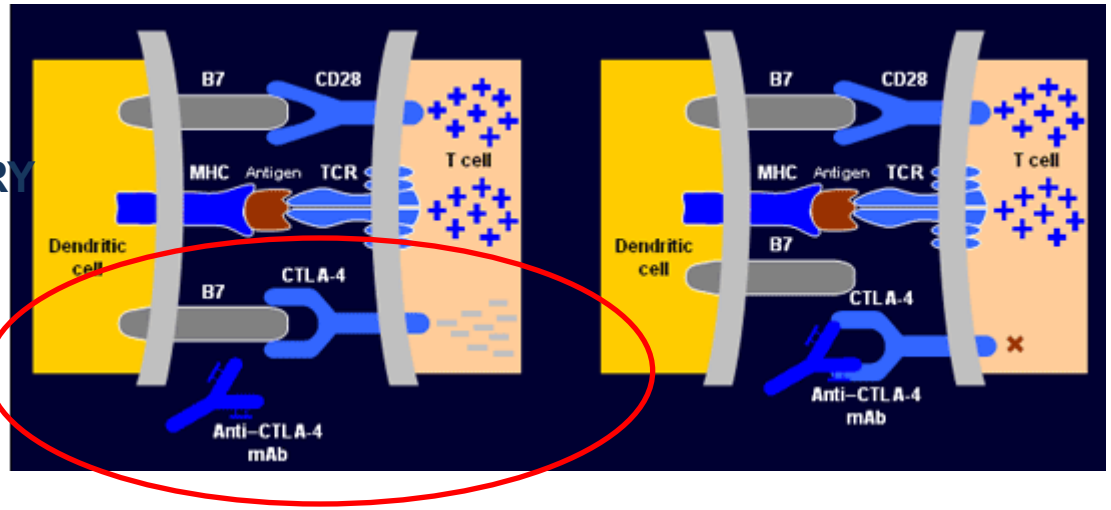
First ranked among the 10 most significant innovations in the year 2013

CER

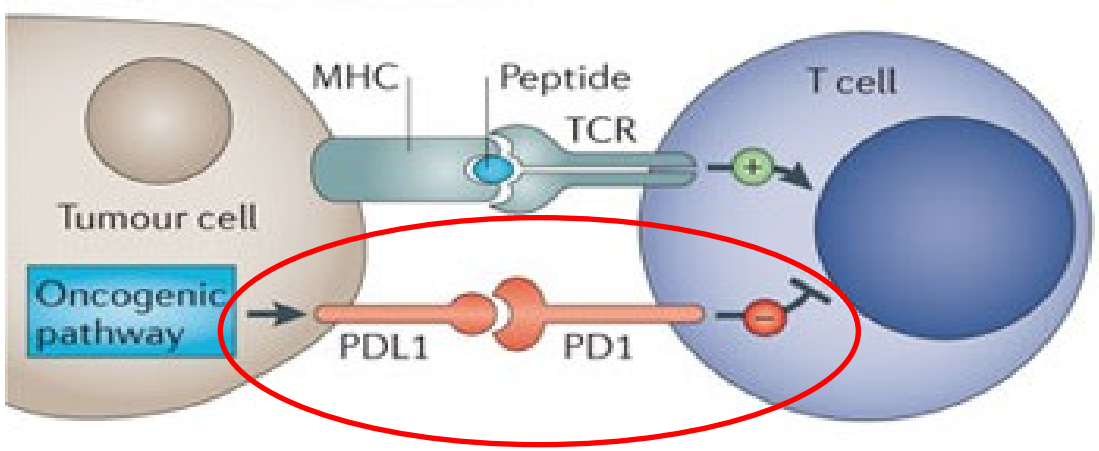
NOTHERAPY

CHECK POINT MODULATORS: CTLA4 and PD1/PDL1

CTLA4 T cell INHIBITORY SYSTEM



PD1/PDL1 T cell INHIBITORY SYSTEM



# of dendritic cells: historical ment of cancer vaccines

DC capture, process and present antigens to lymphocytes

First DC-based clinical trial

R.Steinman: Nobel Prize

1973 1980 1987 1990 1996 2001 2010 2011

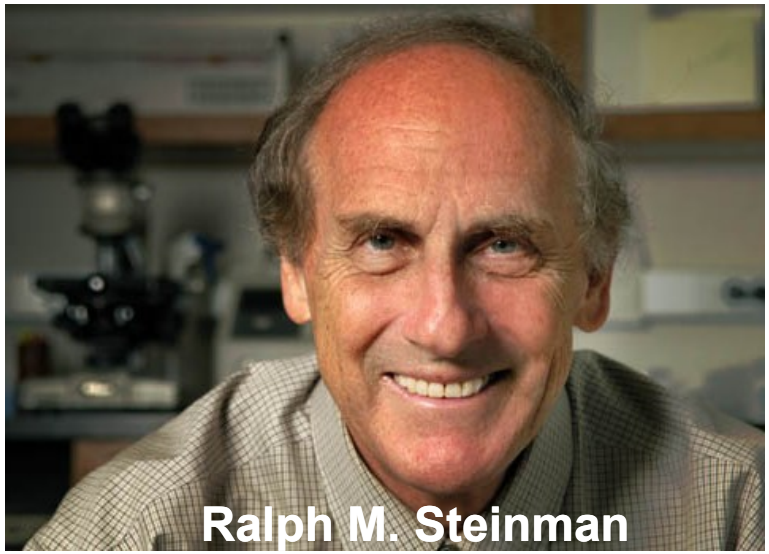
DC discovery

for T cell activation and immunity

DC control immune tolerance

DC are generated in vitro from blood precursors

First APC-based cancer vaccine approved by FDA: Provenge



EMA approved Provenge on 03/10/2013

The marketing authorisation has been withdrawn in EU, at the request of the marketing authorisation holder, on 19/05/2015.

Science "Areas to Watch" 2015:
COMBINED IMMUNOTHERAPY

Science 2013

Sviluppo di vaccini terapeutici mediante l'uso di cellule dendritiche e citochine

Quali prospettive per un loro sviluppo clinico in pazienti oncologici, da soli o in combinazione, nel nuovo scenario dell'onco-immunologia?

Major issues for the development of therapeutic cancer vaccine

1. **Which tumor antigen(s)?**

2. **How to break tolerance and immune escape mechanisms (***which adjuvants and/or combination therapies?)*

- ***Some cytokines (IFN-I) and chemotherapeutic agents as***

«OLD DRUGS FOR A NEW CLINICAL USE»

New rationales for combination, including check-point inhibitors

«Drug repositioning» o rivalutazione farmacologica è un processo che ha coinvolto nel passato un considerevole numero di farmaci per le ragioni più diverse tra cui:

- **Limitazione degli studi precedenti in una direzione ristretta**
- **Sviluppo di nuove conoscenze sui meccanismi di azione**
- **Arresto nello sviluppo per motivi commerciali**
- **Scadenza dei termini brevettuali**

La riconsiderazione di vecchi farmaci per nuovi usi può avere diversi vantaggi:

- **Espansione dello spettro terapeutico**
- **Un'utilizzazione più mirata**
- **Farmacocinetica e sicurezza già definite**
- **Riduzione di costi di ricerca e validazione**

Alcuni esempi storici

- **Digoxin** (Digitalis lanata) formerly used as emetic drug (1600), subsequently used in heart failure and arrhythmia, has recently been postulate, as a phytoestrogen, to have beneficial effect in prostate cancer by suppressing androgen levels.
- **Metformin**, an antidiabetic drug, is now used for endometrial cancer through inhibition of the PI3K-Akt-mTOR pathway by activating LKB1-AMPK and reduction of insulin and insulin-like growth factor-1 due to AMPK activation.
- **Thalidomide**, originally developed as a sedative, it was found to cause serious birth defects. In the ensuing decades it was found to inhibit angiogenesis in animal models and was subsequently shown to have promising therapeutic effect on refractory multiple myeloma and metastatic prostate cancer
- **Chloroquine**, a classical antimalarial drug, is now considered an immuno stimulator and is proposed as anticancer agent
- **Sildenafil** (Viagra), an inhibitor of (cGMP)-specific phosphodiesterase type 5 (PDE5), was originally developed for the treatment of coronary artery disease by Pfizer in 1980s. The side effect of sildenafil, marked induction of penile erections, was serendipitously found during the Phase I clinical trials for the patients with hypertension and angina pectoris.

Drug repurposing in oncology--patient and health systems opportunities

Bertolini F, Sukhatme VP and Bouche, Nat Rev Clin Oncol. 2015

DRUG REPOSITIONING:
Nuove promesse per vecchi farmaci nell'immunoterapia dei tumori

Un esempio

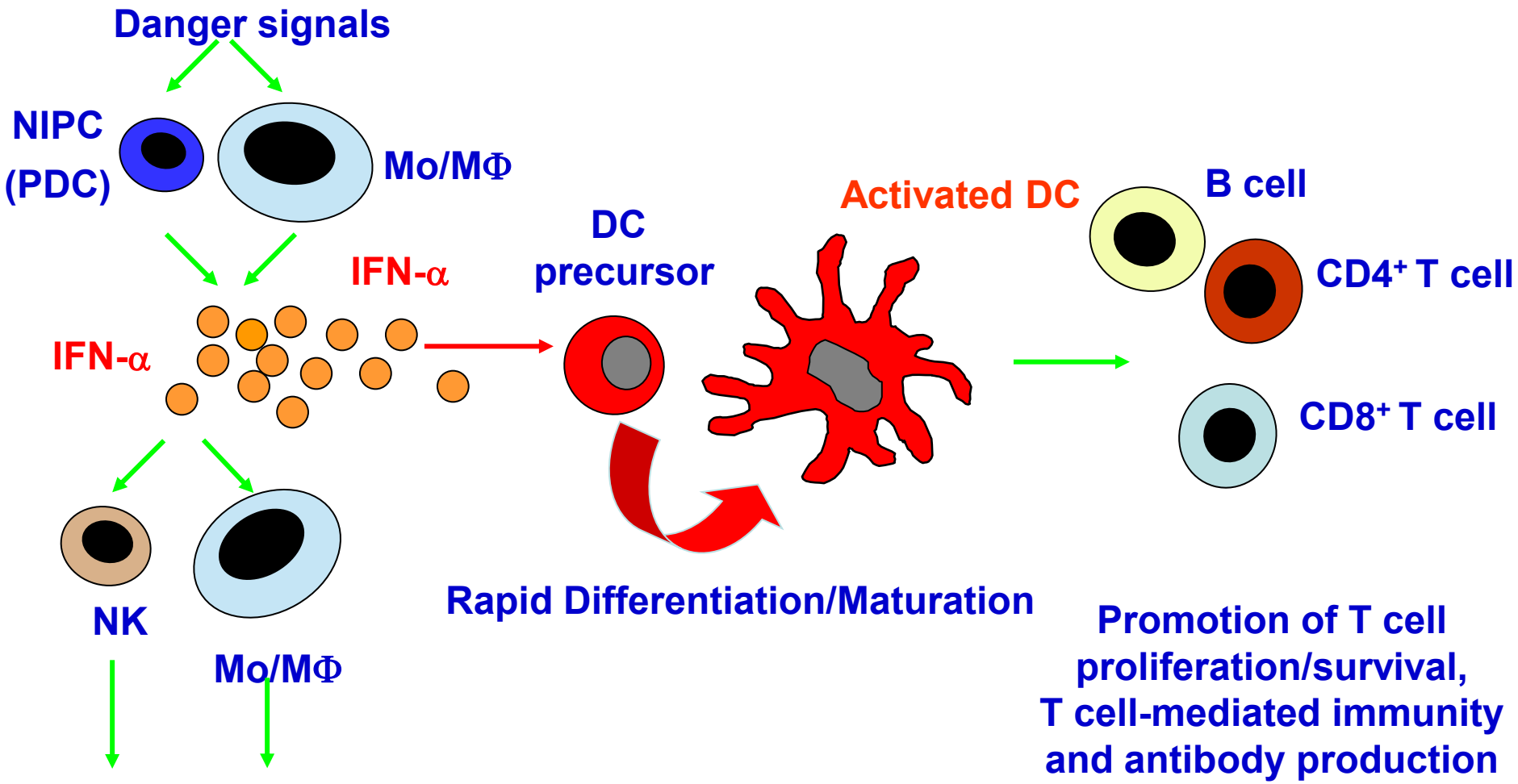
Un farmaco biologico dalle proprietà in continua evoluzione, tradizionalmente usato come antitumorale e antivirale, sul quale l'industria farmaceutica ha apparentemente smesso di investire in termini di ricerca

Interferone di tipo I (α–β)

Proprietà immunomodulanti

- **The generation of a long-lasting antitumor response to type I IFN depended on host immune mechanisms** (*F. Belardelli et al., 1982, ..2002)*
- **IFN-I induces: T cells and Mϕ cytotoxic activity** *(Webb TS 1990),* **activation of Mϕ, NK** *(Trinchieri G 1978)*, **CD8+ memory T cells** *(Tough DF, 1996),* **DC** *(Santini SM,2000),*
- **Plays a key role in Th-1 polarization** *(Brinkmann, 1993),* **in enhancing Ab response** *(Le Bon,2001),* **and de-activating T suppressor functions** *(Pace L, 2010)*
- **IFN-I effects on the innate immune response and on immunological memory can account for its efficacy as a vaccine adjuvant, as demonstrated in an influenza infection model in mice** *(Bracci L, 2006)* **as well as in melanoma patients** *(Di Pucchio T, 2006)*
- **Endogenous IFN-I has a central role in restriction of tumor growth in both mouse and human models** (*Gresser et al., 1983, Dunn et. Al., 2005., Romina et al ., 2017)*
- **Endogenous and exogenous IFN-I plays a crucial role in the induction of immunogenic apoptosis during chemotherapy, thus suppliyng tumor antigens to the system of the innate immunity** *(Sistigu A., 2014)*

IFN-α as an important natural factor linking innate and adaptive immunity



Innate Immunity

Adaptive Immunity + Memory

Towards a local/selective use of IFN-α

IFN-α as a vaccine adjuvant → **Enhanced activity, No toxicity**

Clinical studies on the immune adjuvant activity of IFN-α

- *Di Pucchio T. et al.* Immunization of stage IV melanoma patients with Melan-A/MART-1 and gp100 peptides plus IFN-α results in the activation of specific CD8+ T cells and monocyte/dendritic cell precursors. **Cancer Res**. 66:4943-4951, 2006.

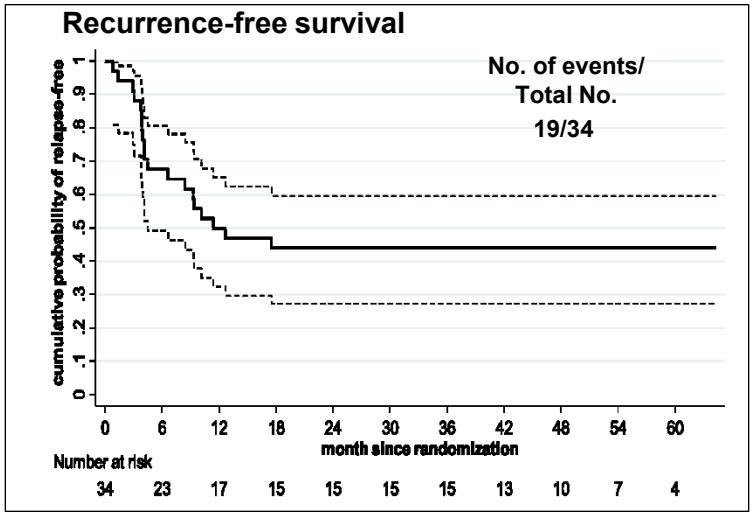
- *Rizza P. et al.* Evaluation of the effects of human leukocyte IFN-α on the immune response to the HBV vaccine in healthy unvaccinated individuals. **Vaccine** 26:1038-1049, 2008.

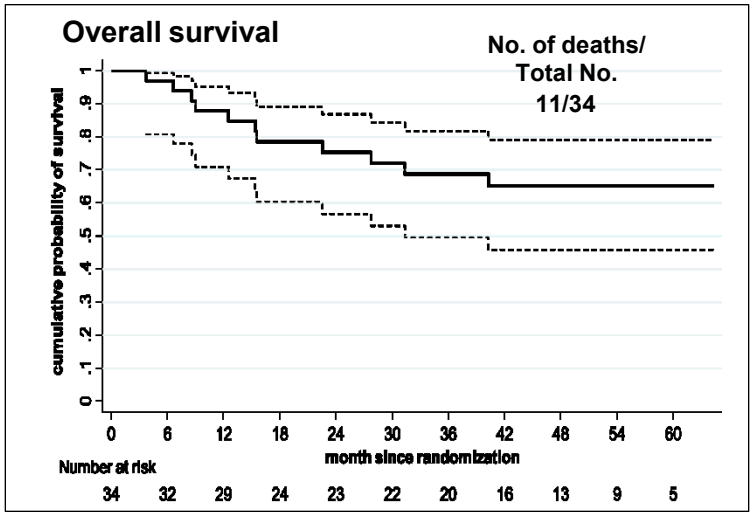
- *Miquilena-Colina M.E. et al.* Recombinant interferon-alpha2b improves immune response to hepatitis B vaccination in haemodialysis patients: results of a randomised clinical trial. **Vaccine** 27:5654-60, 2009.

IFN-α in combinazione con un vaccino peptidico in pazienti con melanoma ad alto rischio (Urbani et al., manoscritto in preparazione)

Phase II clinical study

Stage III-IV melanoma pt. treated with peptide-based vaccination + type I IFN

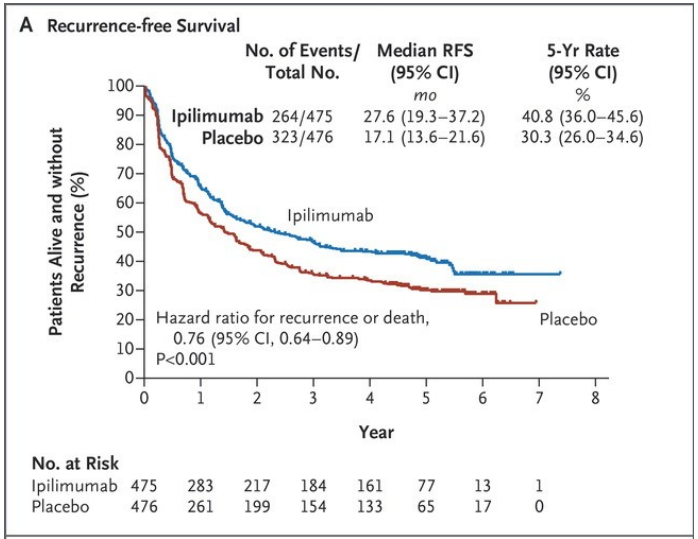


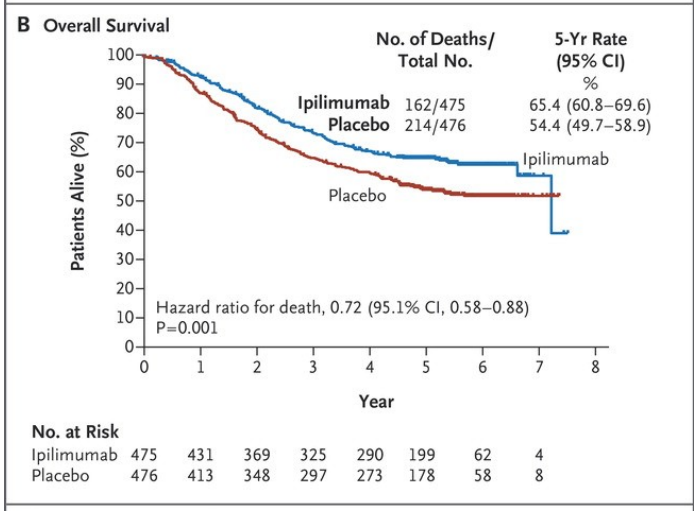


Urbani F et al., Manuscript in preparation

Phase III clinical study

Stage III melanoma pt. treated with Ipilimumab





Eggermont AM et al. N Engl J Med. 2016

Poster N. 44.

DRUG REPOSITIONING: Nuove promesse per vecchi farmaci nell'immunoterapia dei tumori

L. Bracci, F. Moschella, E. Proietti, Dip. Oncologia e Medicina Molecolare, Istituto Superiore di Sanità

Poster N. 14.

IFN-α potenzia gli effetti antitumorali diretti e immunomediati dei farmaci epigenetici verso le cellule metastatiche e staminali del tumore al colon-retto.

M. Buoncervello[1], S. Parlato[1], G. Romagnoli[1], A. Fragale[1], I, Canini[1], E. Toschi[1], M. Buccarelli[1], M. Falchi[2], A. De Ninno[3], R. Molfetta[4], D. Macchia[1], M. Spada[1], M. Biffoni[1], R. Paolini[4], E. Martinelli[5], A. Sgambato[6], D. Lucchetti[6], I. Capone[1], F. Belardelli[1], L. Businaro[3], L. Ricci Vitiani[1] & L. Gabriele[1]

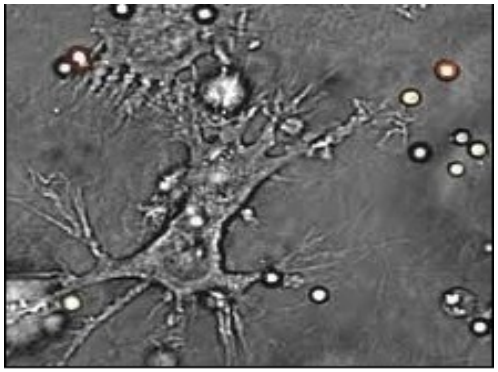
[1] Dipartimento di Oncologia **e** Medicina Molecolare, ISS, Roma; [2] Centro Nazionale AIDS, ISS, Roma; [3]Istituto di Fotonica e Nanotecnologie, CNR, Roma; [4]Istituto Pasteur, Fondazione Cenci Bolognetti, Università di Roma Sapienza; [5]Dipartimento di Ingegneria Elettronica, Università di Roma Tor Vergata; [6]Istituto di Patologia Generale, Università Cattolica del Sacro Cuore, Roma.

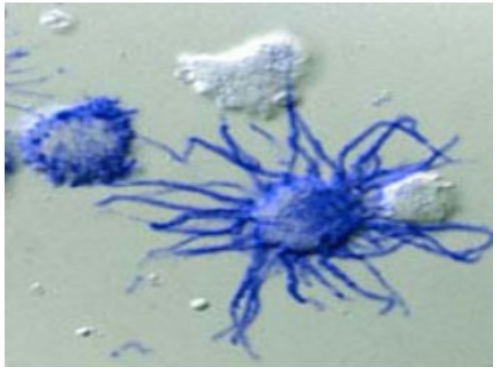
DENDRITIC CELLS-BASED VACCINATION IN CANCER PATIENTS

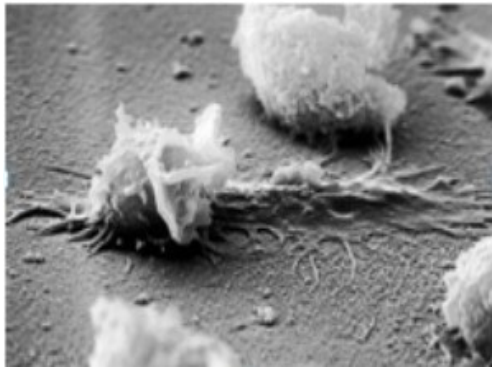
What have we learned so far?

- DC-based vaccines are safe and induce a frequency of T lymphocyte response higher than that obtained by peptide-based vaccines and adjuvants;

- Different DC can induce different (even opposite) effects.







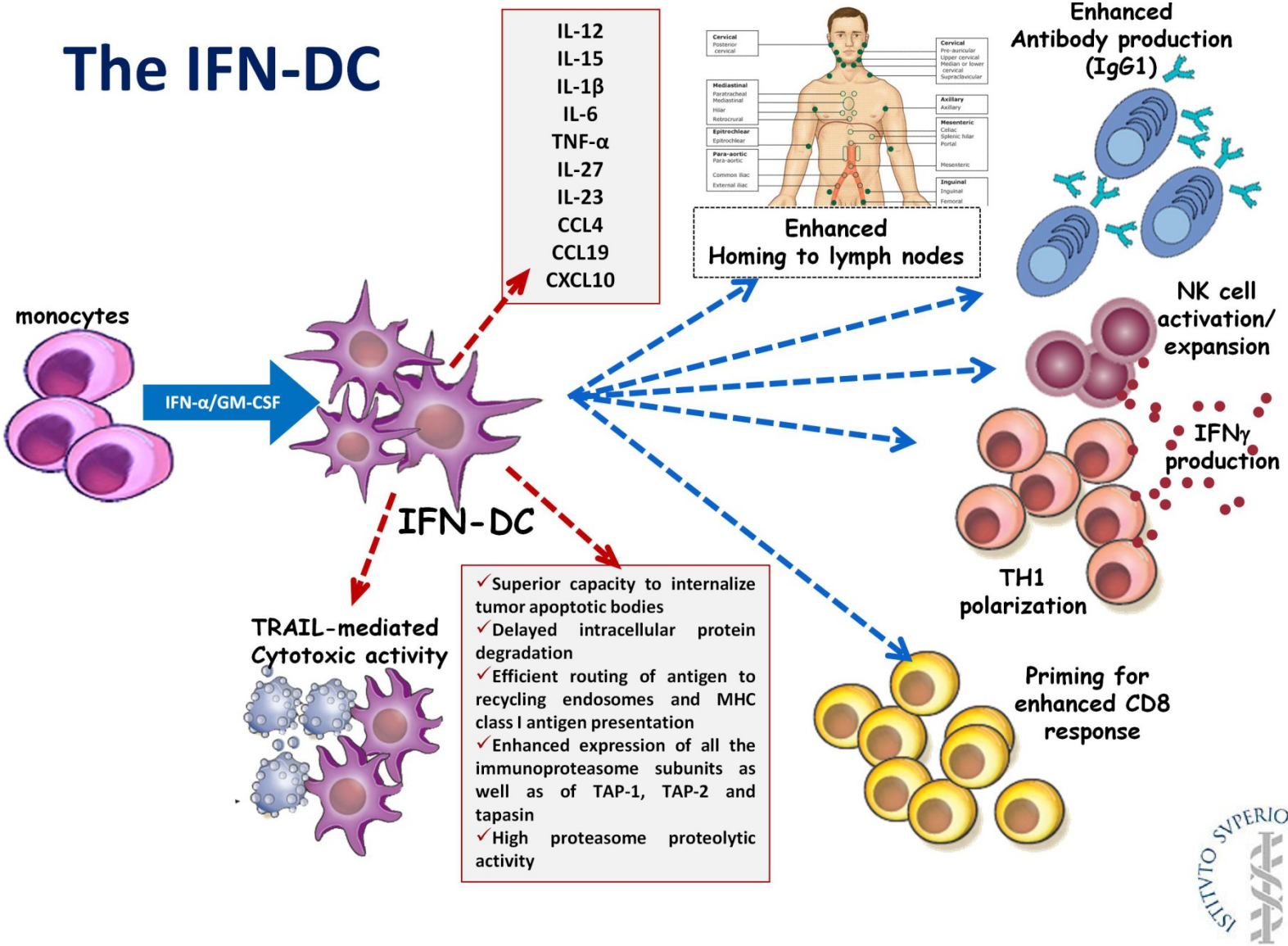
poster n°13

Istituto Superiore di Sanità

IFN-DC: un nuovo farmaco cellulare autologo per l'immunoterapia dei tumori sviluppato all'ISS e in fase di sperimentazione clinica.

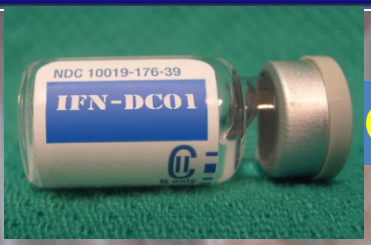
[1]Santini S.M., [1]Lapenta C., [2]Santodonato L., [2]D'Agostino G., [1]Donati S., [2]Montefiore E., [2]Carlei D, [2]Monque D., [2]Napolitano M., [1]Lattanzi L., [1]Urbani F., [1]Macchia I., [1]Spadaro F., [2]Aricò E., [3]Spada M., [1]Proietti E., [4]Cox M.C., [5]Belardelli F., [1]Capone I., [2]Rozera C.

The IFN-DC


IL-12
IL-15
IL-1β
IL-6
TNF-α
IL-27
IL-23
CCL4
CCL19
CXCL10
Enhanced Homing to lymph nodes
Enhanced Antibody production (IgG1)
monocytes
IFN-α/GM-CSF
IFN-DC
NK cell activation/ expansion
IFNγ production
TH1 polarization
Priming for enhanced CD8 response
TRAIL-mediated Cytotoxic activity
✓Superior capacity to internalize tumor apoptotic bodies
✓Delayed intracellular protein degradation
✓Efficient routing of antigen to recycling endosomes and MHC class I antigen presentation
✓Enhanced expression of all the immunoproteasome subunits as well as of TAP-1, TAP-2 and tapasin
✓High proteasome proteolytic activity

IFN-DC in patients with advanced melanoma

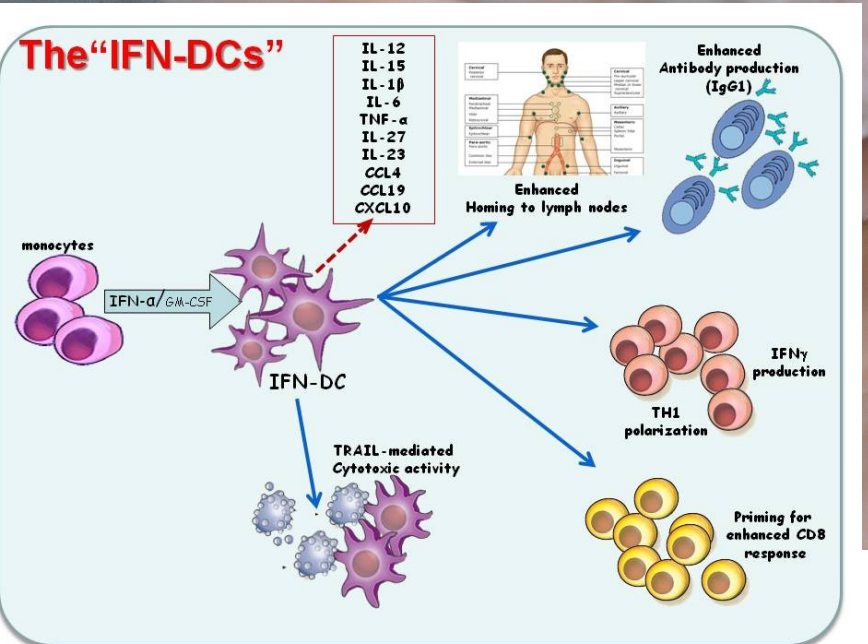
Dendritic cell-based immunotherapy one day after chemotherapy (dacarbazine) in patients with metastatic melanoma: a phase I study

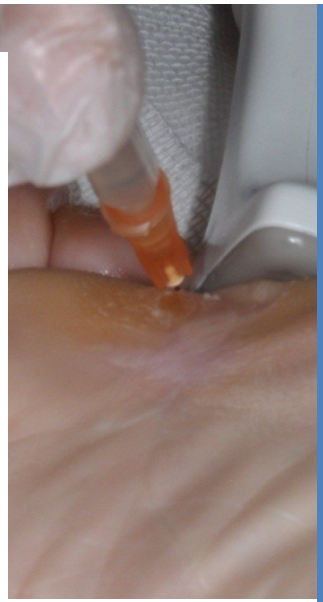


GMP production: FaBioCell, ISS; Clinical Center: IDI, Rome

Intratumoral injection of IFN-alpha dendritic cells after dacarbazine activates anti-tumor immunity: results from a phase I trial in advanced melanoma.

Rozera C. et al. J Transl Med. 2015 May 2;13:139.





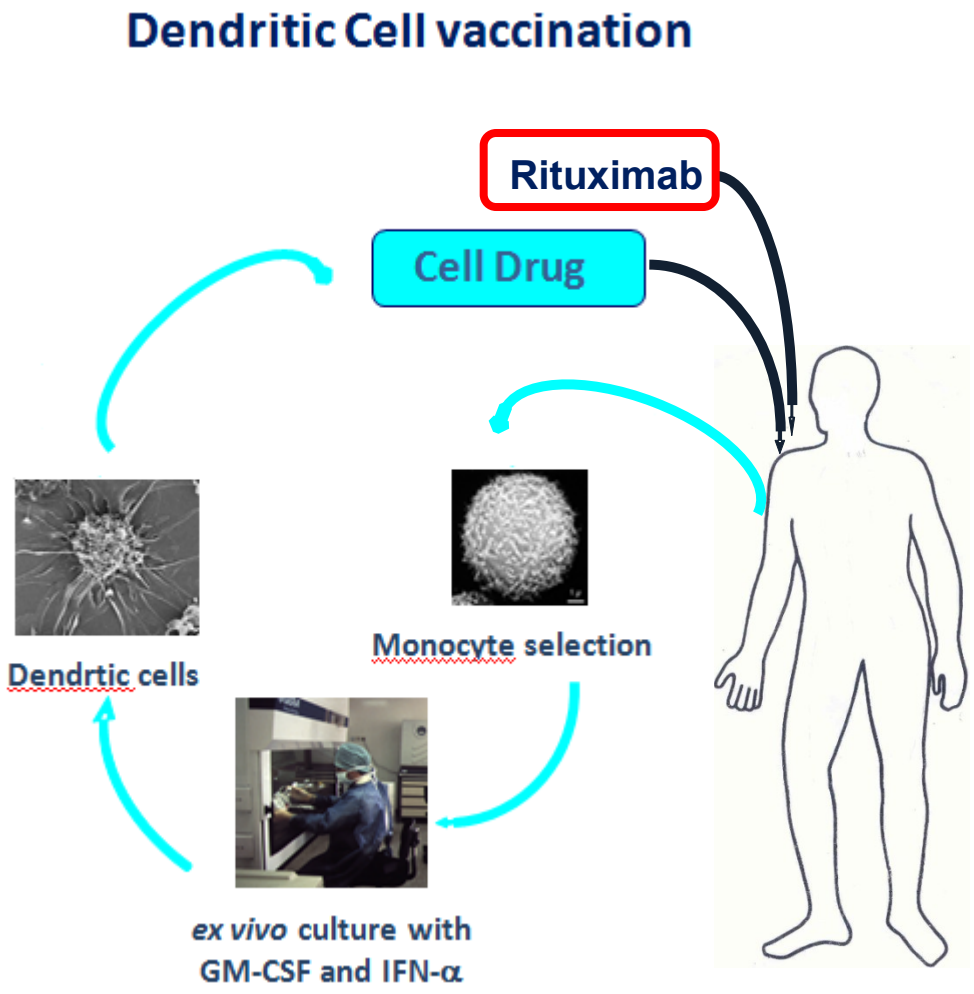
- Primary end point: safety

Rationale for potential efficacy:

- Direct TRAIL-mediated killing
- Capture of apoptotic bodies by IFN-DC and tumor antigen processing
- Tumor antigen presentation and activation of effector and memory T lymphocytes
- Anti-tumor immune response

Phase I Clinical Study - NHL-IFN-DC-2

IFN-DC-based immunotherapy in combination with Rituximab in indolent non-Hodgkin lymphoma patients



Intratumoral DC injection

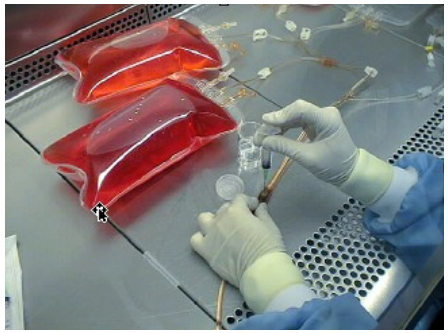
- **Primary end point: safety**

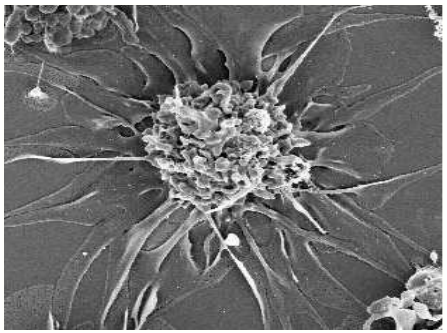
Rationale for potential efficacy:

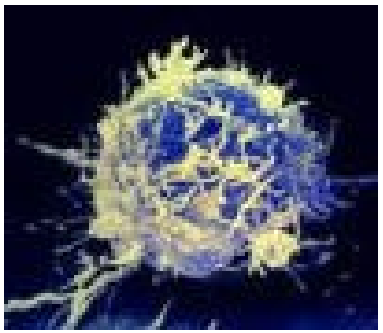
- **Direct TRAIL-mediated killing**
- **Capture of apoptotic bodies by IFN-DC and tumor antigen processing**
- **Tumor antigen presentation and activation of effector and memory T lymphocytes**
- **Anti-tumor immune response**

FaBioCell: products and activities (Poster 28)

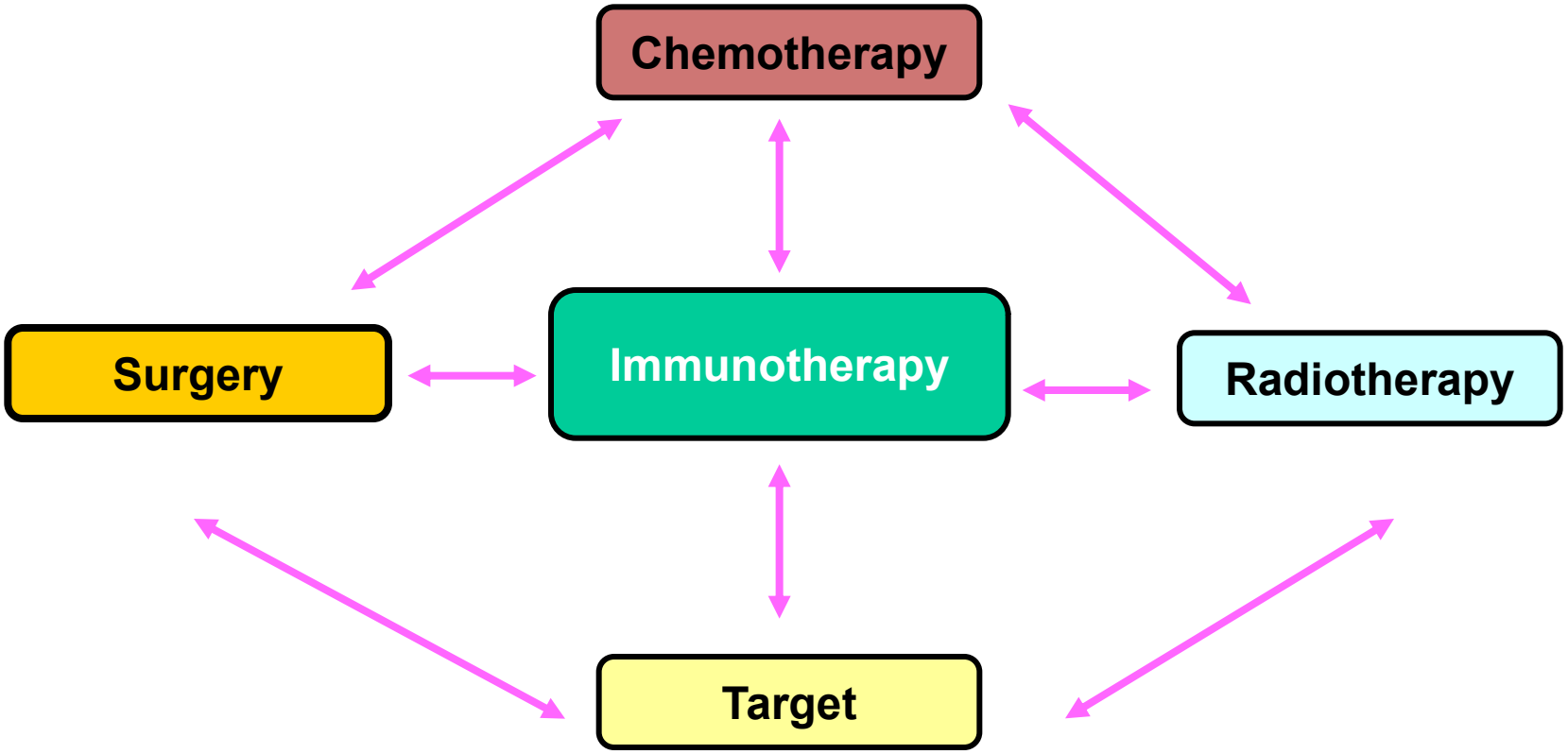
- **Autologous cell drugs:**
  - **Dendritic Cells** (Melanoma, Follicular lymphomas, Cervical cancer)
  - **In vitro expanded NK Cells** (ALL patients) – Prof. R. Foà, Università La Sapienza, Roma
  - ……



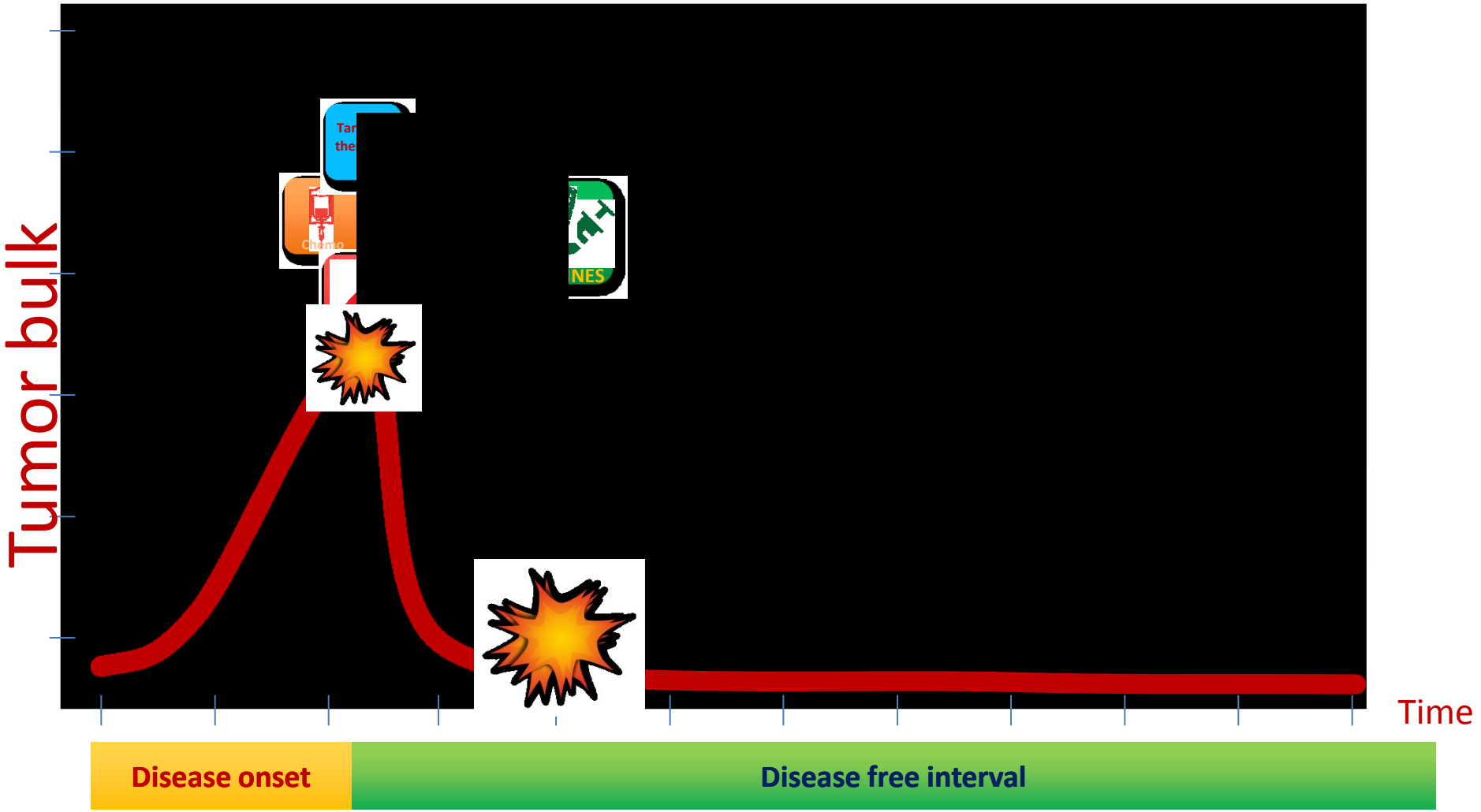




Therapeutic combinations



VACCINES for tertiary prevention of cancer



Alcune Considerazioni Finali

Nuovi razionali per terapie combinate (onco-immunologia)

Verso un'onco-immunologia personalizzata con nuove prospettive per ottenere risposte durature e prevenzione delle recidive, che deve essere di ampio accesso per i pazienti, tenendo anche conto dei costi e della sostenibilità per i SSN

Vaccini terapeutici basati su semplici e rapidi protocolli di DC autologhe attivate o vaccini sintetici basati su un nuovo uso di citochine (es. IFN) o nuove formulazioni possono trovare modalità di uso clinico, in combinazione con nuovi farmaci, inclusi gli anticorpi immunomodulanti

Importanza delle collaborazioni tra i diversi attori pubblici e privati nell'interesse dei pazienti e la salute pubblica

Istituto Superiore di Sanità
Dip. di Oncologia e Medicina Molecolare

Principali studi preclinici sulle DC
- S.Santini
- C. Lapenta
- L. Lattanzi
- F. Spadaro
- S. Donati

Modelli preclinici e Disegno studi clinici
- L. Bracci,
- F. Moschella,
- L. Gabriele
- P. Rizza
- P. Sestili
- V. La Sorsa
- I. Capone

- E. Proietti

Monitoraggio studi clinici
- E. Aricò
- F. Urbani
- I. Macchia
-

FaBioCell
- C. Rozera
- L. Santodonato
- G. D'Agostino
- E. Montefiore
- M. Napolitano
- D. Monque
- D. Carlei

Istituto Dermopatico dell'Immacolata (IDI), Roma
- P. Marchetti
- G. C. Antonini Cappellini

Azienda Ospedaliera Sant'Andrea Roma
- M. C. Cox
- A. Pavan
- I. Casorelli
- M. Mattei
- S. Vaglio
- G. Natale
- C. Berdini

Istituto Tumori Regina Elena (Roma)
- P. Nisticò,
- V. Ferraresi
- F. Cognetti

Sviluppo di vaccini terapeutici mediante l'uso di cellule dendritiche e citochine

GRAZIE PER L'ATTENZIONE!

"Le nuove sfide della ricerca oncologica: verso una partnership tra Enti Pubblici e Industria nella regione Lazio"

Roma, 17 maggio 2017

REGIONE LAZIO

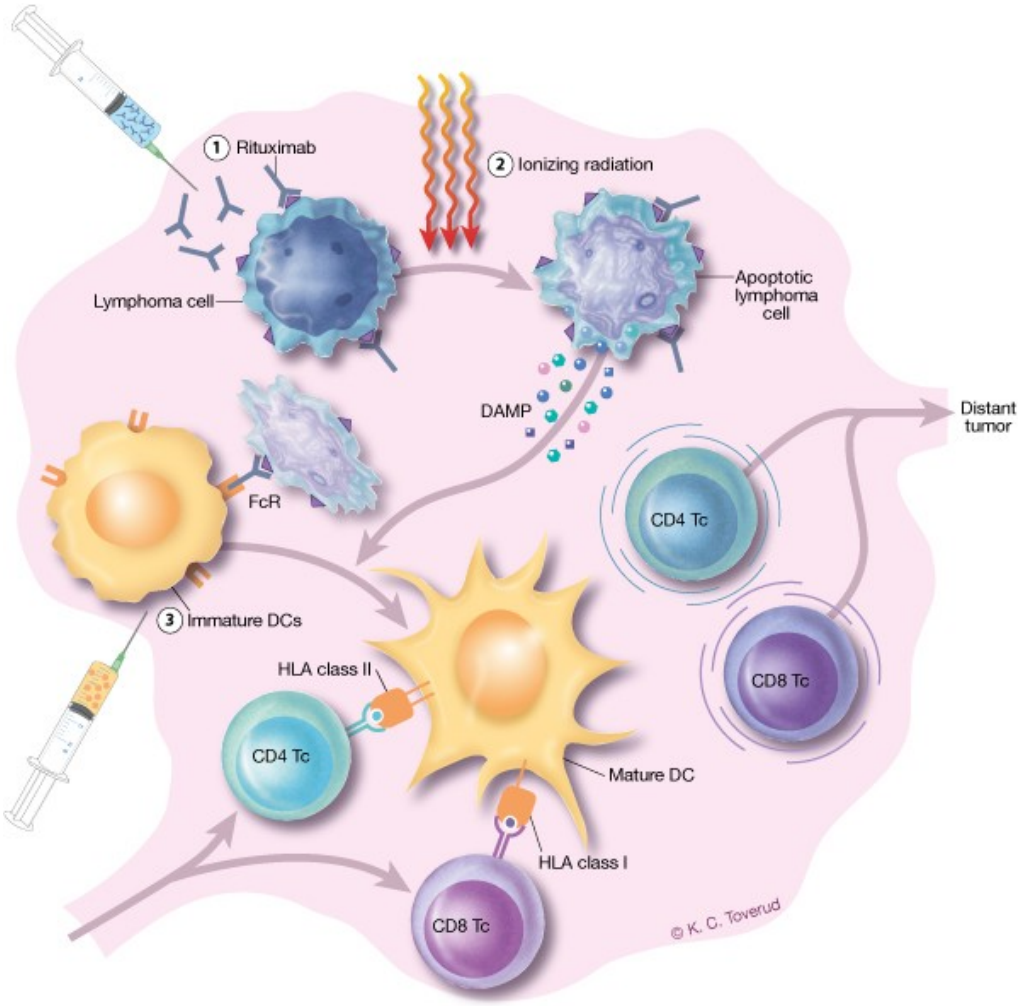
ISTITUTO SUPERIORE DI SANITÀ

LAZIO INNOVA

Sequential intranodal immunotherapy induces anti-tumor immunity and correlated regression of disseminated follicular lymphoma

Arne Kolstad, Shraddha Kumari, Mateusz Walczak, Ulf Madsbu, Trond Hagtvedt, Trond Velde Bogsrud, Gunnar Kvalheim, Harald Holte, Ellen Aurlien, Jan Delabie, Anne Tierens and Johanna Olweus

Blood. Jan 1;125(1):82-9. 2015



- ✓ 14 patients with stage III/IV follicular lymphoma were enrolled
- ✓ 5 patients (36%) displayed objective clinical response
- ✓ 2 patients had durable complete remissions.

Key Points

- Local immunotherapy induced systemic responses in patients with disseminated FL.
- Clinical responses correlated with systemic antitumor T-cell immunity.

Strong rationale for combining DC vaccination and immunomodulating antibodies (or other "immunological" treatments)

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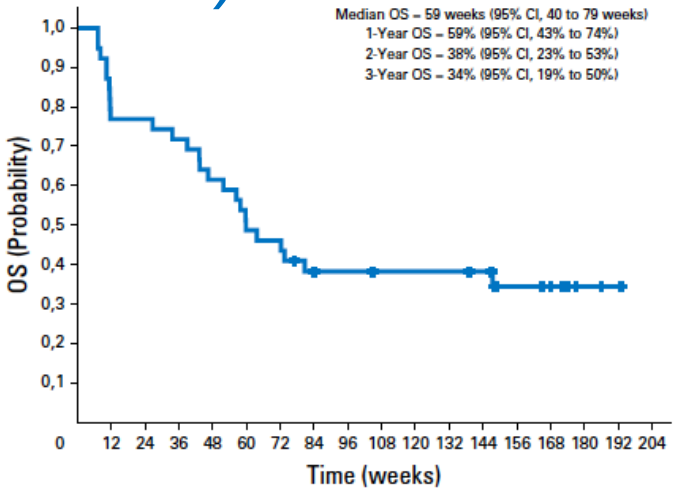
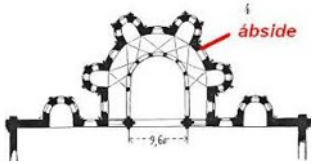
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

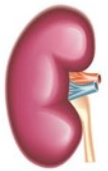
Phase II Study of Autologous Monocyte-Derived mRNA Electroporated Dendritic Cells (TriMixDC-MEL) Plus Ipilimumab in Patients With Pretreated Advanced Melanoma

Sofie Wilgenhof, Jurgen Corthals, Carlo Heirman, Nicolas van Baren, Sophie Lucas, Pia Kvistborg, Kris Thielemans, and Bart Neyns





ABSIDE: ABscopal effect IFN-α Dendritic Cells
Pazienti con melanoma metastatico o avanzato non resecabile



Renal-Vax: DC vaccination plus High-dose IL-2 and immunomodulating RT in metastatic renal cell carcinoma refractory to TKI

MESO-VAX: DC vaccination combined with pembrolizumab in PD-L1 negative refractory mesothelioma ***Under submission***

COMBO-MEL: DC vaccination combined with PD-1 blockade in PD-L1 negative metastatic melanoma
In preparation

Medical Needs nella terapia del cancro

Terapie Specifiche
Terapie Personalizzate
Strategie di Prevenzione Terziaria

L'impegno ISS per lo sviluppo di farmaci cellulari e vaccini terapeutici

Ricerca di base
e traslazionale

li
ci

Ricerca di base e traslazionale
Stefano M. Santini
Caterina Lapenta
Simona Donati
Francesca Spadaro
Laura Lattanzi
Massimo Spada

Studi clinici
Enrico Proietti
Imerio Capone
Filippo Belardelli

FaBioCell
Carmela Rozera
Laura Santodonato
Giuseppina D'Agostino
Enrica Montefiore
Mariarosaria Napolitano
Domenica Monque
Davide Carlei
Paola Rizza

Strategie future e progettualità con le IFN-DC: Il successo nel trattamento dei pazienti oncologici mediante immunoterapia sarà sempre più strettamente dipendente dallo sviluppo di combinazioni sinergiche di vaccinazione e strategie in grado di ripristinare e/o migliorare le risposte immunitarie.

Interazioni strategiche di ISS con partners clinici e aziende biofarmaceutiche

Sostenibilità e finanziamenti della ricerca preclinica:

- Tumor vaccines of all types and dendritic cell-based therapies to induce or amplify tumor immunity (Progetto di Ricerca Finalizzata)
- Preclinical Studies On The Potential Beneficial Effects Of Lenalidomide On The Immune Response To Follicular Lymphoma Elicited By Therapeutic Cancer Vaccines
- Pembrolizumab to enhance the immune response to follicular lymphoma elicited by IFN-DC based immunization in vitro and in humanized animal models
- Novel Cell Products And Strategies For Improving Adoptive Cell Transfer Therapy For Follicular Lymphoma

Drug repurposing in oncology--patient and health systems opportunities

Bertolini F, Sukhatme VP and Bouche, Nat Rev Clin Oncol. 2015

In most countries, healthcare service budgets are not likely to support the current explosion in the cost of new oncology drugs. Repurposing the large arsenal of approved, non-anticancer drugs is an attractive strategy to offer more-effective options to patients with cancer, and has the substantial advantages of cheaper, faster and safer preclinical and clinical validation protocols. The potential benefits are so relevant that funding of academically and/or independently driven preclinical and clinical research programmes should be considered at both national and international levels. To date, successes in oncology drug repurposing have been limited, despite strong evidence supporting the use of many different drugs. A lack of financial incentives for drug developers and limited drug development experience within the non-profit sector are key reasons for this lack of success. We discuss these issues and offer solutions to finally seize this opportunity in the interest of patients and societies, globally.

IFN-DC: Farmaci Cellulari e Vaccini Terapeutici

Background scientifico: Le principali aree di ricerca del gruppo hanno incluso tradizionalmente studi sul ruolo di IFN di tipo I nel controllo della crescita neoplastica, studi sui meccanismi di azione antitumorale di IFN e suo utilizzo nella terapia genica del cancro, immunologia e immunoterapia dei tumori

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Anno 2000 - Sviluppo e caratterizzazione delle IFN-DC (cell drug). ***[J Exp Med. 2000; 191:1777-88]*** **– I nostri studi hanno dimostrato come l'esposizione dei monociti di sangue periferico all'IFN-α in combinazione con GM-CSF determini il loro rapido differenziamento in cellule dendritiche (IFN-DC). Le IFN-DC esibiscono un fenotipo parzialmente maturo, caratteristiche delle DC mieloidi, plasmacitoidi e cellule natural killer, favoriscono la risposta T-helper 1 (Th1) e l'attivazione dell'immunità cellulo-mediata.**

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Brevetto USA e PCT (Assignee: Istituto Superiore di Sanità)
Method for generating highly active human dendritic cells from monocytes

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FaBioCell **Trial clinici**

- **phase I clinical study in chemo-immunotherapy of advanced melanoma (EudraCT no.2010-018675-18).** *Rozera C et.al. Intratumoral injection of IFN-alpha dendritic cells after dacarbazine activates anti-tumor immunity: results from a phase I trial in advanced melanoma. J Transl Med. 2015;13:139.*
- **phase I clinical trial in follicular lymphoma patients (EudraCT no.2013-003158-25) - In corso**

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Ricerca traslazionale

Biologia delle IFN-DC
Vaccini terapeutici
Adoptive Cell Transfer

L'impegno ISS per lo sviluppo di nuove opportunità terapeutiche

Esistono evidenze sperimentali e cliniche che indicano come l'immunoterapia attiva con vaccini tumorali sia in grado di indurre una risposta immune contro il tumore. Tale risposta è inibita dall'attività immunosoppressiva del microambiente tumorale e da meccanismi regolatori che coinvolgono l'ingaggio di molecole checkpoint del sistema immunitario.

IMMUNOTERAPIA ATTIVA

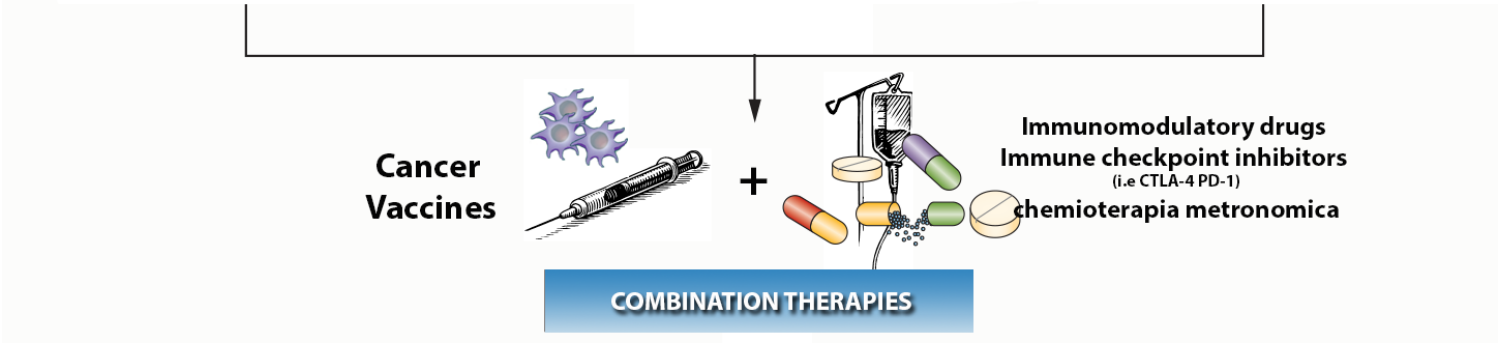
I vaccini terapeutici hanno il compito di indurre e/o rafforzare la risposta immunitaria specifica contro il tumore ovvero verso gli antigeni specifici o associati al tumore stesso.

La risposta immune al tumore è indebolita o inibita dall'attività immunosoppressiva del microambiente tumorale e da meccanismi regolatori che coinvolgono l'ingaggio di molecole checkpoint del sistema immunitario

IMMUNOTERAPIA IMMUNOMODULANTE

I farmaci immunomodulanti e gli inibitori del checkpoint immunitario funzionano in maniera aspecifica, amplificando la risposta immune, bloccando i circuiti di controllo ed inibizione dell'intero complesso delle risposte immunitarie di un individuo.

Il meccanismo d'azione degli inibitori, presenta il rischio di indurre iperattività del sistema immunitario e gravi reazioni immunopatologiche.



Proprietà immunomodulanti

- **The generation of a long-lasting antitumor response to type I IFN depended on host immune mechanisms** *F. Belardelli et al. Interferon-alpha in tumor immunity and immunotherapy, Cytokine Growth Factor Rev (2002)*
- **IFN-I induces: T cells and Mϕ cytotoxic activity** *(Webb TS 1990),* **activation of Mϕ, NK** *(Trinchieri G 1978)*, **CD8+ memory T cells** *(Tough DF, 1996),* **DC** *(Santini SM,2000),*
- **Plays a key role in Th-1 polarization** *(Brinkmann, 1993),* **in enhancing Ab response** *(Le Bon,2001),* **and de-activating T suppressor functions** *(Pace L, 2010)*
- **IFN-I effects on the innate immune response and on immunological memory can account for its efficacy as a vaccine adjuvant, as demonstrated in an influenza infection model in mice** *(Bracci L, 2006)* **as well as in melanoma patients** *(Di Pucchio T, 2006) (Gogas H, J. 2006)*
- **Endogenous or exogenous IFN-I has a central role in the induction of immunogenic apoptosis during chemotherapy, thus suppliyng tumor antigens to the system of the innate immunity** *(Sistigu A., 2014)*

Cancer cell-autonomous contribution of IFN-1 signaling to the efficacy of chemotherapy

A. Sistigu et al. Nat Med. 2014 Nov;20(11):1301-9

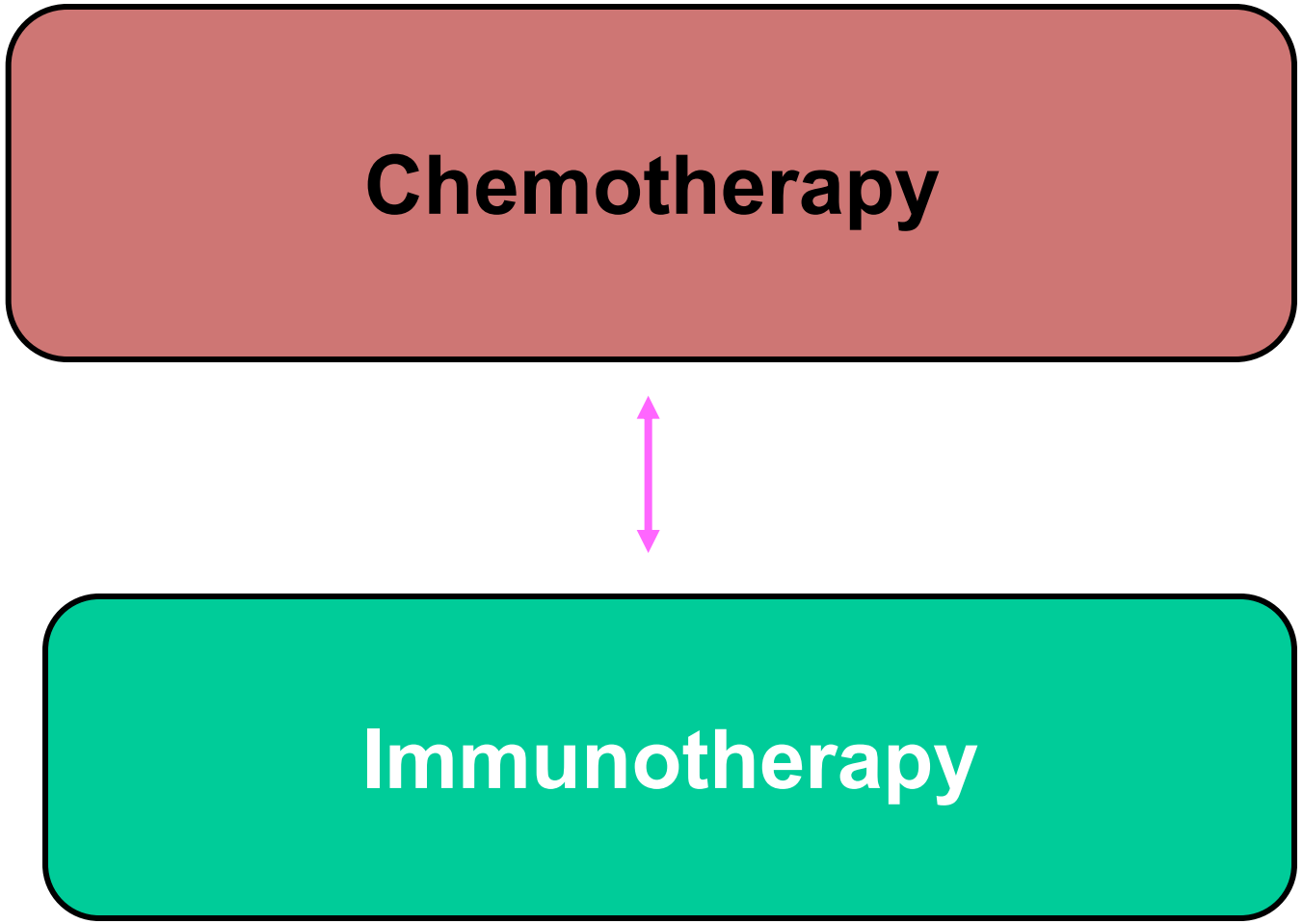
Some of the anti-neoplastic effects of anthracyclines in mice originate from the Induction of innate and T cell-mediated anticancer immune responses. Here we demonstrate that anthracyclines stimulate the rapid production of type I IFNs by malignant cells after activation of the endosomal pattern recognition receptor Toll-like receptor 3 (TLR3). By binding to IFN-α and IFN-β receptors (IFNARs) on neoplastic cells, type I IFNs trigger autocrine and paracrine circuitries that result in the release of chemokine (C-X-C motif) ligand 10 (CXCL10). Tumors lacking Tlr3 or Ifnar failed to respond to chemotherapy unless type I IFN or Cxcl10, respectively, was artificially supplied. Moreover, a type I IFN-related signature predicted clinical responses to anthracycline-based chemotherapy in several independent cohorts of patients with breast carcinoma characterized by poor prognosis. Our data suggest that anthracycline-mediated immune responses mimic those induced by viral pathogens. We surmise that such 'viral mimicry' constitutes a hallmark of successful chemotherapy.

Interferons and the Immunogenic Effects of Cancer Therapy

Andy J. Minn[1,*]

Trends in Immunology, November 2015, Vol. 36, No. 11

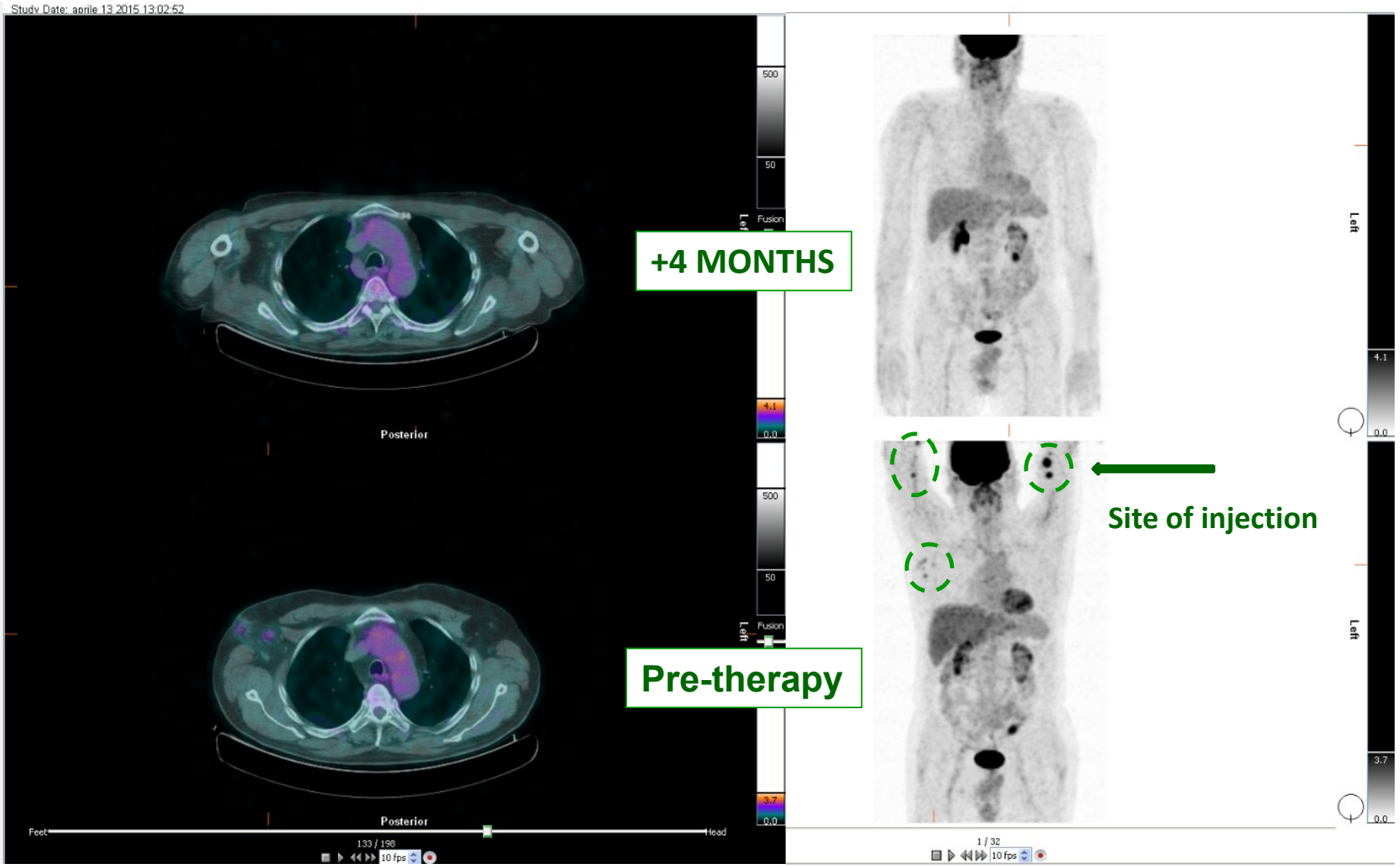
Alcuni chemioterapici agiscono mediante attivazione del sistema immune, inducendo un'apoptosi immunogenica e citochine (es. IFN) con funzioni chiave



IFN-I: target in movimento con molteplici effetti e meccanismi, a volte di tipo «paradosso»

IFN-α come adiuvante di una risposta immune contro il tumore: evidenze in modelli sperimentali e clinici

PET- SCAN



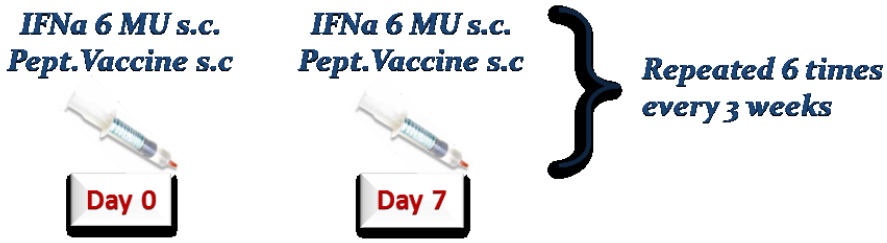
ID	Diagnosis	Age	Sex	Previous Treatment	Disease status
DSFA01	FL	60	M	RCHOP/HDT-BMT	Relapse #3

Somministrazione refratta di IFN e vaccino

(in pazienti con melanoma)

Treatment schedule

(Melan-A + NYESO-1)



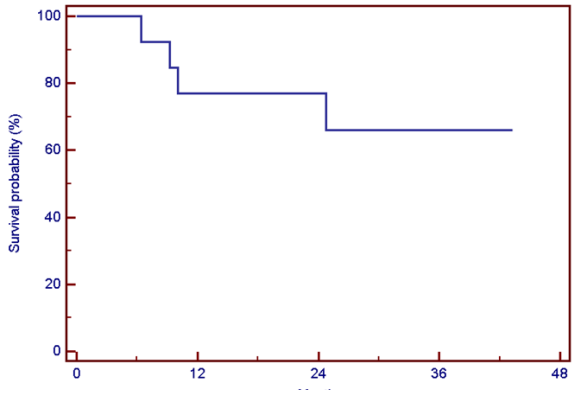
Patients

Stage	N. of patients	Relapsing	dead
III b-c	9	3	0
IV m1a-m1b	4	0	0
Total	13	3	0

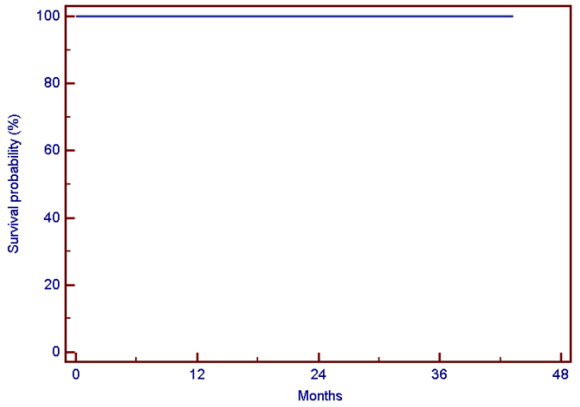
Kaplan-Meier curves (per protocol)

Average follow up: 40 months (36-48)

Relapse-free survival



Overall survival



IFN-I: target in movimento con molteplici effetti e meccanismi, a volte di tipo «paradosso»

Effetto paradosso di una produzione cronica di IFN
o di over-esposizione a dosi elevate in grado di indurre
up-regolazione di PD-1/PDL-1 e quindi immunosoppressione

Combination Cancer Therapies with Immune Checkpoint Blockade: Convergence on Interferon Signaling

Cell *165*, April 7, 2016 ©2016

Andy J. Minn[1,3,4,*] and E. John Wherry[2,3]

Improving efficacy of immune checkpoint blockade for cancer can be facilitated by combining these agents with each other and/or with other conventional or targeted therapies. Interferon and innate immune signaling pathways in immune and tumor cells have emerged as intriguing determinants of response and resistance, often in complex and seemingly paradoxical ways.