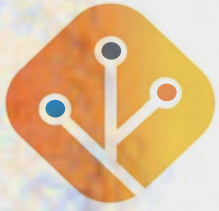
Hot Topic:

Designing nanomedicine for immune-oncology

March 20, 2017



MARBLE CENTER FOR CANCER NANOMEDICINE

Small technologies, **BIG** impact

KOCH INSTITUTE for Integrative Cancer Research at MIT

nature biomedical engineering

PERSPECTIVE

PUBLISHED: 10 FEBRUARY 2017 | VOLUME: 1 | ARTICLE NUMBER: 0029

Designing nanomedicine for immuno-oncology

Wen Jiang[1*], Christina A. von Roemeling[2,3,4], Yuanxin Chen[2,3,4], Yaqing Qie[2,3,4], Xiujie Liu[2,3,4], Jianzhu Chen[5] and Betty Y.S. Kim[2,3,4*]

Two major obstacles facing cancer nanomedicine are the tendency of nanoparticles to be taken up by normal tissues and organs and the nanoparticles' inability to efficiently penetrate solid tumours. Although substantial efforts have been made to improve the intratumoural delivery of nanotherapeutics, many strategies have failed to produce meaningful clinical benefits. Recent advances in the field of immuno-oncology have led to drugs that boost the host's own immune system to fight cancer. In contrast to conventional therapies, which often target cancer cells, immunotherapies stimulate immune cells in ways that promote their recognition and the eradication of tumours. In this Perspective, we posit that this approach represents a new framework for cancer nanomedicine, and that immune-targeted nanomedicines could generate tumouricidal effects without the need to overcome the pathophysiological barriers that are intrinsic to the tumour microenvironment and that hinder nanoparticle delivery. The rational design of new immuno-oncology nanomedicines provides opportunities for developing the next generation of nanotherapeutics for cancer patients.

Source: Jiang, W. et al. Nature Biomedical Engineering (2017)

Shifting the design strategy of nanomedicines

- Current approaches for intratumoral drug delivery have limited success in the clinic:
  - Physiological barriers
  - Vascular/EPR heterogeneity
  - Drug resistance

Shifting the design strategy of nanomedicines

Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seiichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan

Abstract | Targeting nanoparticles to malignant tissues for improved diagnosis and therapy is a popular concept. However, after surveying the literature from the past 10 years, only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour. This has negative consequences on the translation of nanotechnology for human use with respect to manufacturing, cost, toxicity, and imaging and therapeutic efficacy. In this article, we conduct a multivariate analysis on the compiled data to reveal the contributions of nanoparticle physicochemical parameters, tumour models and cancer types on the low delivery efficiency. We explore the potential causes of the poor delivery efficiency from the perspectives of

Delivery efficiency and consequences

How many nanoparticles accumulate in a tumour? Upon systemic administration, the mononuclear phagocytic system (MPS) and the renal clearance pathway compete with the tumour for nanoparticles. The MPS is a network of organs (most notably the liver and spleen) that contains phagocytic cells that take up nanoparticles, while the renal (kidney) system excretes nanoparticles smaller than 5.5 nm in hydrodynamic diameter[26–29]. Nanoparticles that escape the aforementioned biological barriers have the opportunity to interact with the tumour tissue. The percentage of administered nanoparticles that can achieve this is defined as the nanoparticle delivery efficiency[30].

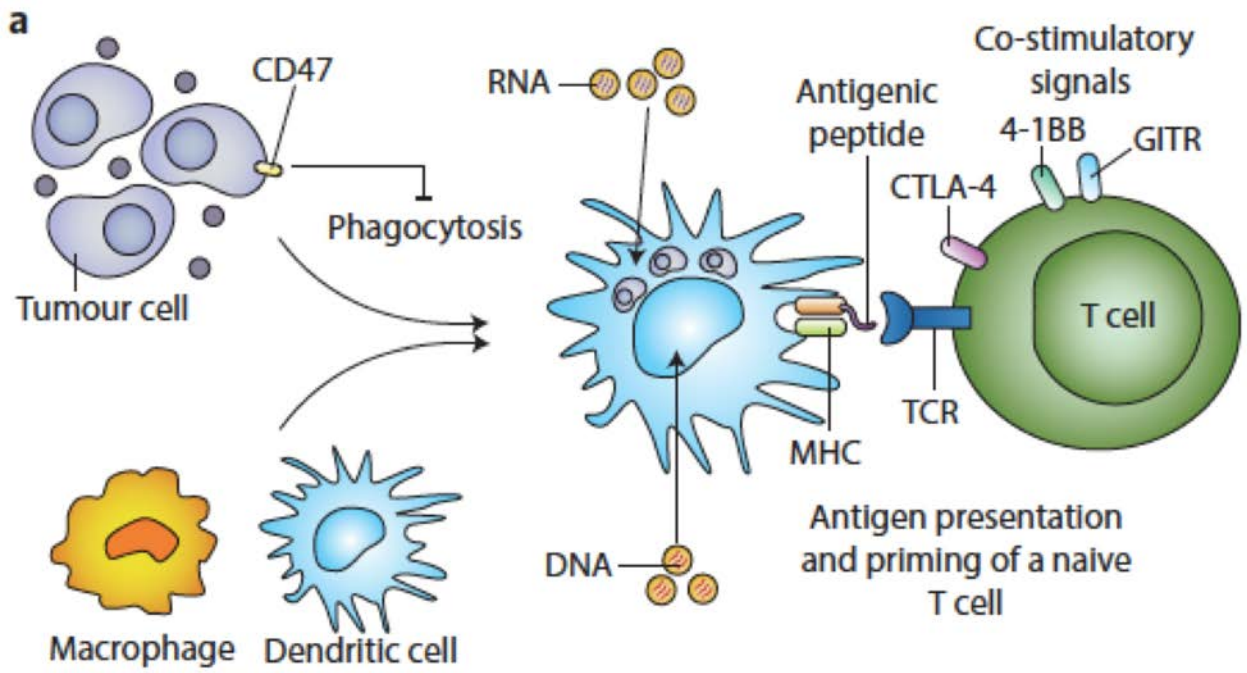
To determine the current delivery efficiency to solid tumours, we used SciFinder and Google Scholar databases

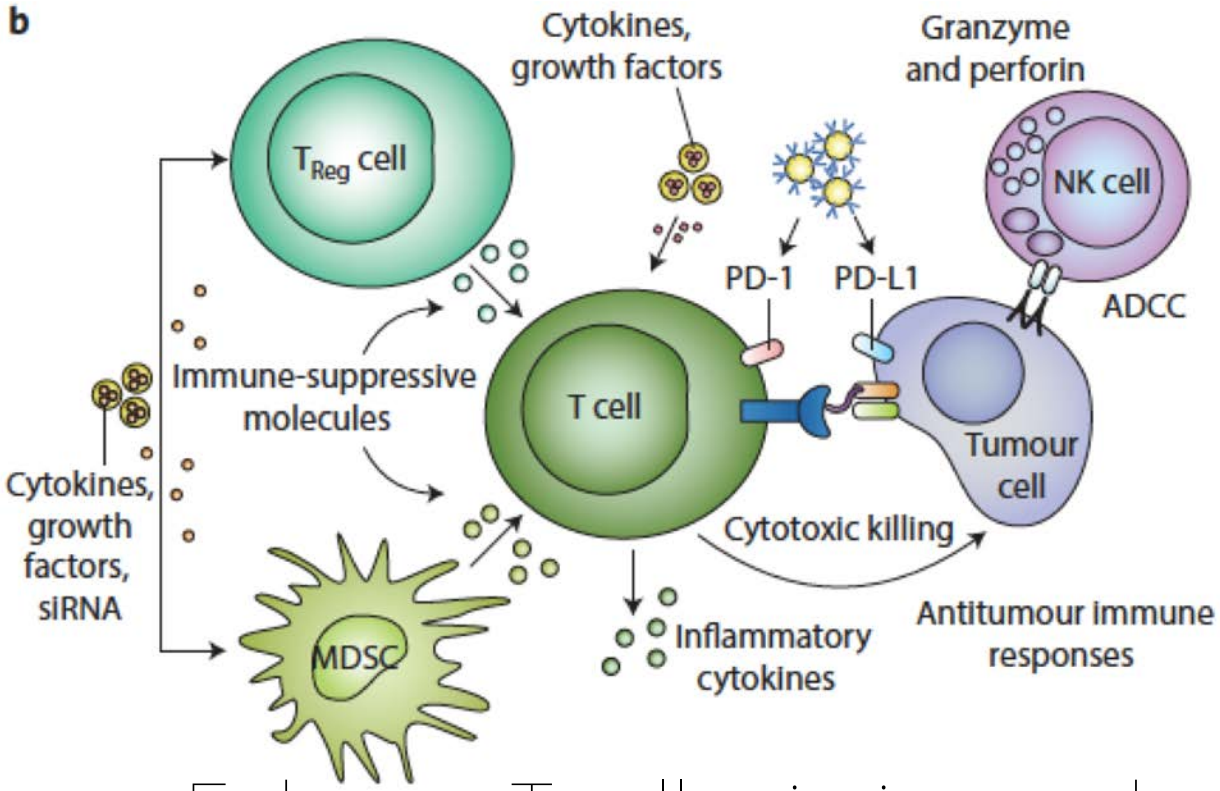
Source: Wilhelm, W. et al. Nature Materials (2016)

Shifting the design strategy of nanomedicines

Authors argue that effective therapies may not require for the nanoparticle to enter the tumor; rather, the nanoparticle can be designed to prime antitumor immunity far from the site of the disease.

Stimulating the immune system to generate a robust anti-tumor response



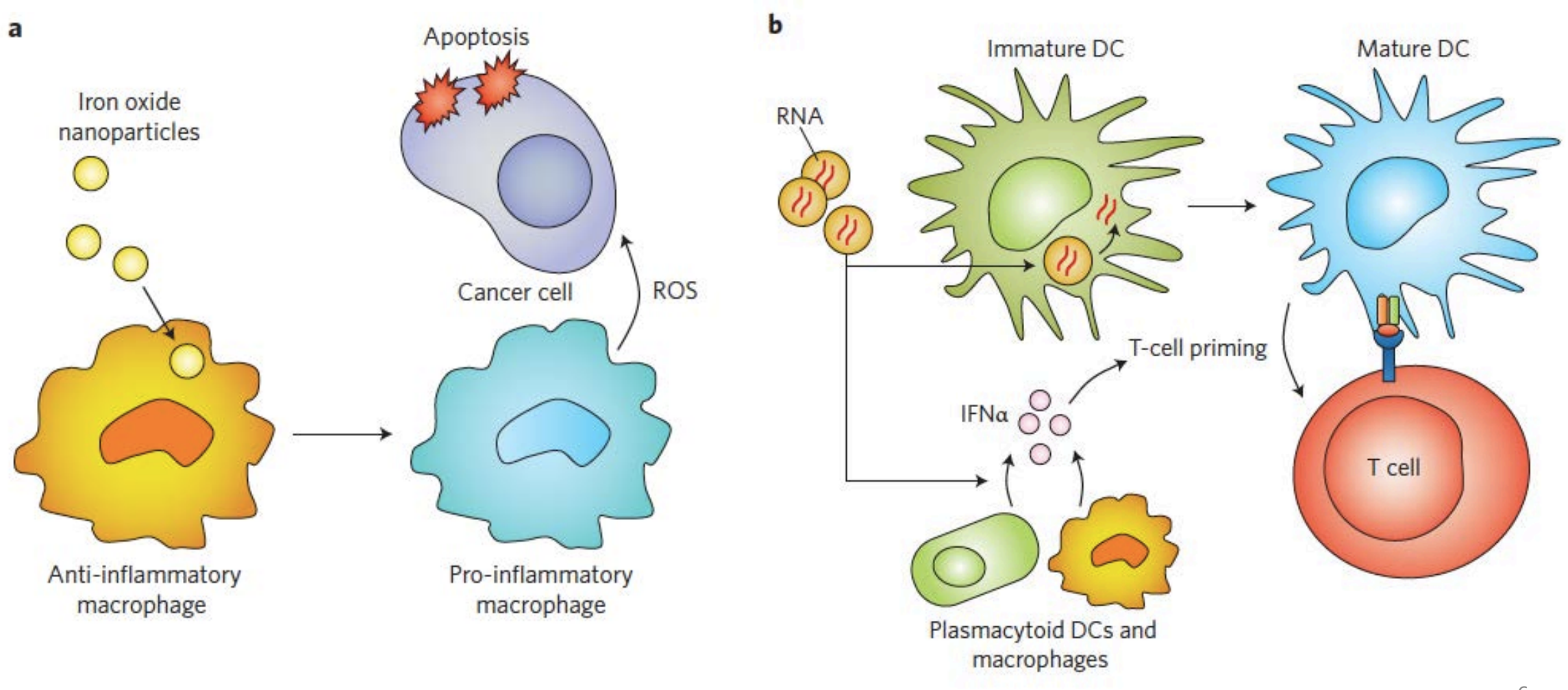


Target antigen presenting cells

Enhance T cell priming and activation

Source: Jiang, W. et al. Nature Biomedical Engineering (2017)

Nanomedicine strategy to enhance antitumor immune response



Source: Jiang, W. et al. Nature Biomedical Engineering (2017)

Nanomedicine strategy to enhance antitumor immune response

ARTICLES
PUBLISHED ONLINE: 26 SEPTEMBER 2016 | DOI: 10.1038/NNANO.2016.168
nature nanotechnology

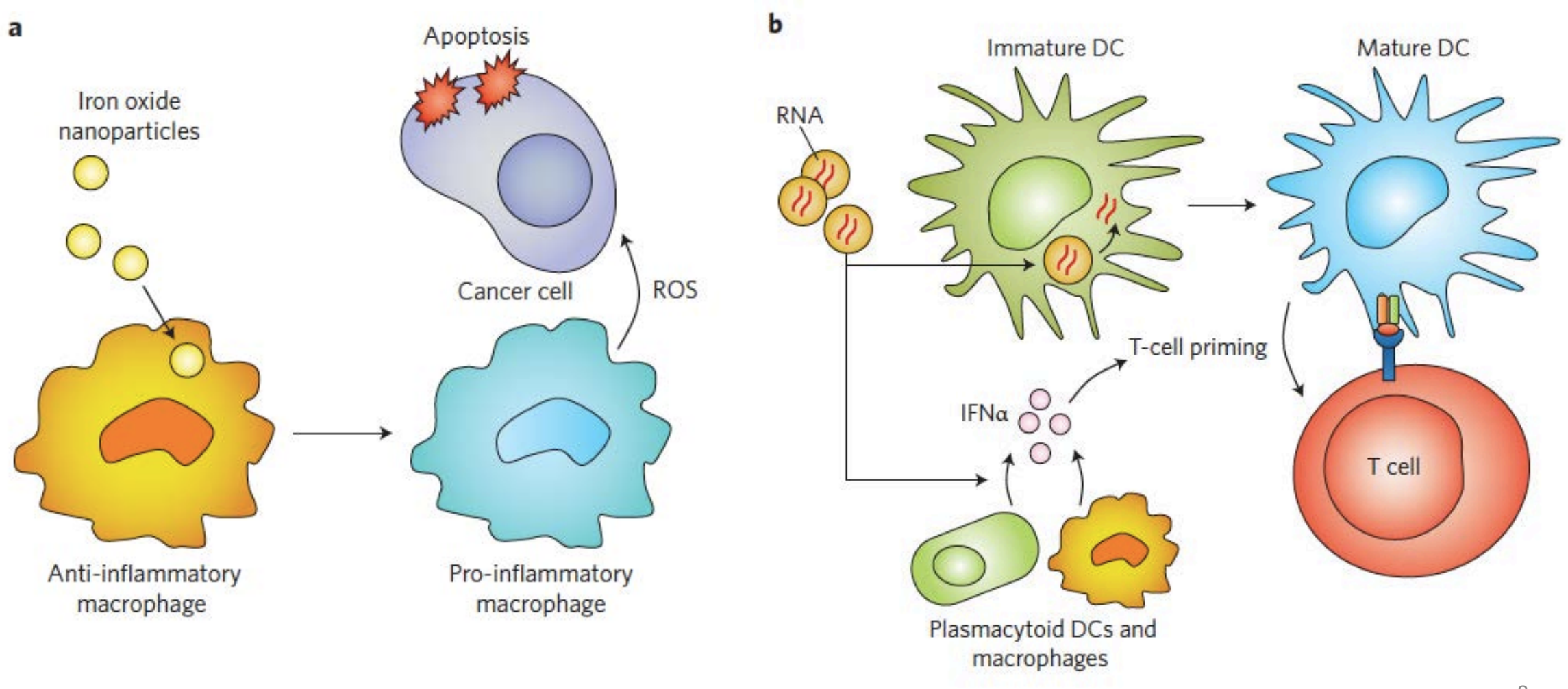
Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues

Saeid Zanganeh[1,2], Gregor Hutter[2,3], Ryan Spitler[1], Olga Lenkov[1,2], Morteza Mahmoudi[4], Aubie Shaw[5], Jukka Sakari Pajarinen[6], Hossein Nejadnik[1,2], Stuart Goodman[6], Michael Moseley[1], Lisa Marie Coussens[5] and Heike Elisabeth Daldrup-Link[1,2,7]*

Until now, the Food and Drug Administration (FDA)-approved iron supplement ferumoxytol and other iron oxide nanoparticles have been used for treating iron deficiency, as contrast agents for magnetic resonance imaging and as drug carriers. Here, we show an intrinsic therapeutic effect of ferumoxytol on the growth of early mammary cancers, and lung cancer metastases in liver and lungs. *In vitro*, adenocarcinoma cells co-incubated with ferumoxytol and macrophages showed increased caspase-3 activity. Macrophages exposed to ferumoxytol displayed increased mRNA associated with pro-inflammatory Th1-type responses. *In vivo*, ferumoxytol significantly inhibited growth of subcutaneous adenocarcinomas in mice. In addition, intravenous ferumoxytol treatment before intravenous tumour cell challenge prevented development of liver metastasis. Fluorescence-activated cell sorting (FACS) and histopathology studies showed that the observed tumour growth inhibition was accompanied by increased presence of pro-inflammatory M1 macrophages in the tumour tissues. Our results suggest that ferumoxytol could be applied 'off label' to protect the liver from metastatic seeds and potentiate macrophage-modulating cancer immunotherapies.

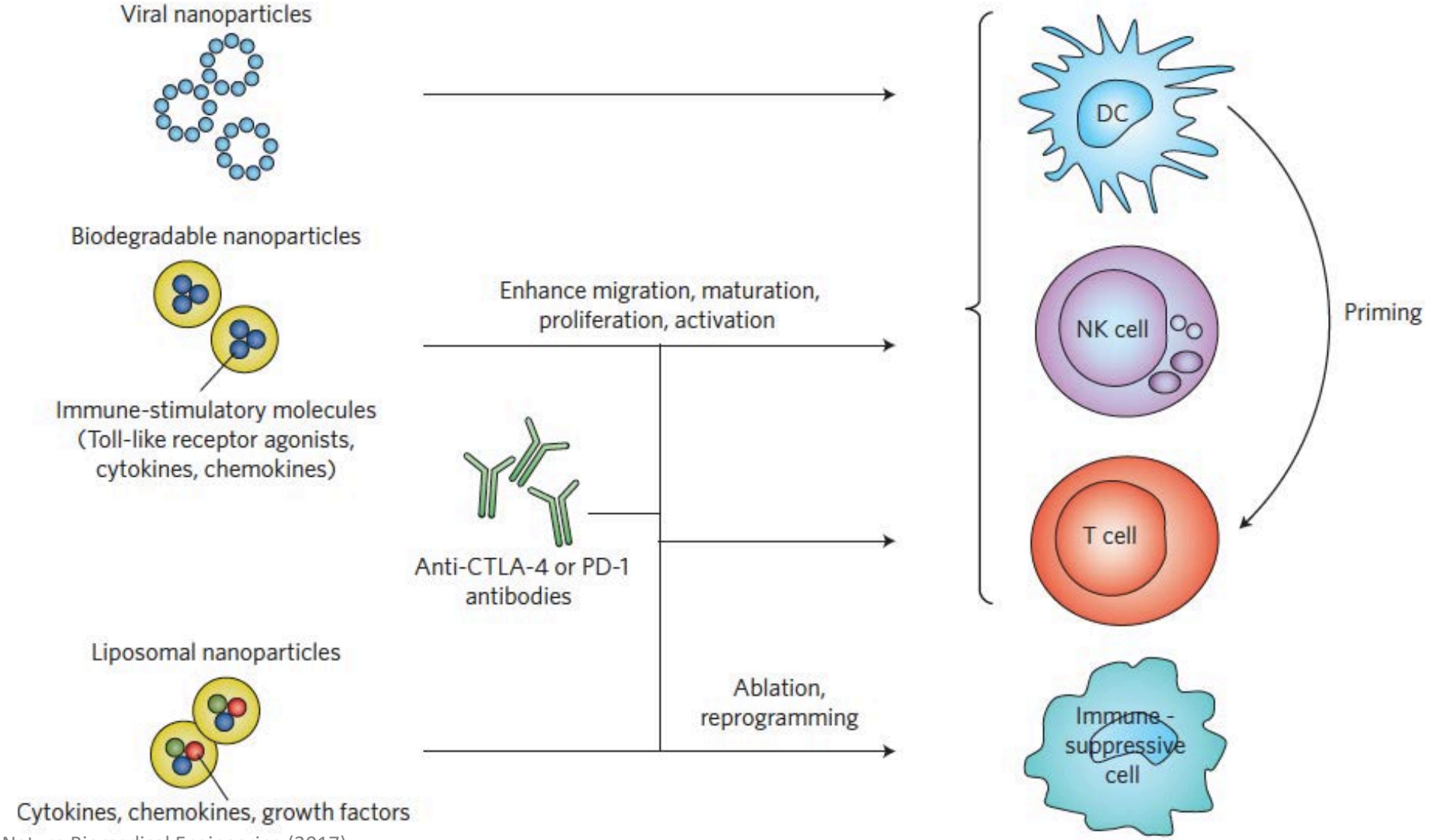
Source: Zanganeh, S. et al. Nature Nanotechnology (2016)

Nanomedicine strategy to enhance antitumor immune response



Source: Jiang, W. et al. Nature Biomedical Engineering (2017)

Nanomedicine strategy to enhance antitumor immune response



Source: Jiang, W. et al. Nature Biomedical Engineering (2017)

Take home

- (keep it constructive/optimistic)

Discussion Questions

- Is activating the immune system necessarily a prerequisite of successful cancer therapy? (think of an example)

Discussion Questions

- Would an immune-engineering approach using nanoparticles represent "a major deviation from the design strategy of current cancer nanomedicine?"