DIRNANO

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Nanovaccines targeting dendritic cells and their potential in cancer immunotherapy

The fast development of novel drugs and technologies have undoubtedly impacted healthcare across the globe. One of most striking successes of modern medicine is unquestionably the development of vaccines which have not only dropped the incidence of severe disease of many pathologies and proved to be essential in control of pandemic such as COVID-19 but have also been essential in eradicating deathly diseases such as smallpox [1].
Vaccines can act on either preventing disease or strongly attenuating its morbidity, thus improving patients' lives while simultaneously relieving the financial burden on the healthcare services.

The underlying concepts of vaccination extend beyond prevention and highlight how boosting the hosts' own immune defence against specific pathogens can shape the course of a disease with their potential application also to non-infectious pathologies. Consequently, it comes to no surprise that developing a vaccine to treat established malignancies has a been an extremely ambitious goal pursued by scientists since the very beginning of 20th century when William Coley injected tumors with killed Streptococcus and Serratia [2].

Immunotherapy in cancer: successes and current bottlenecks

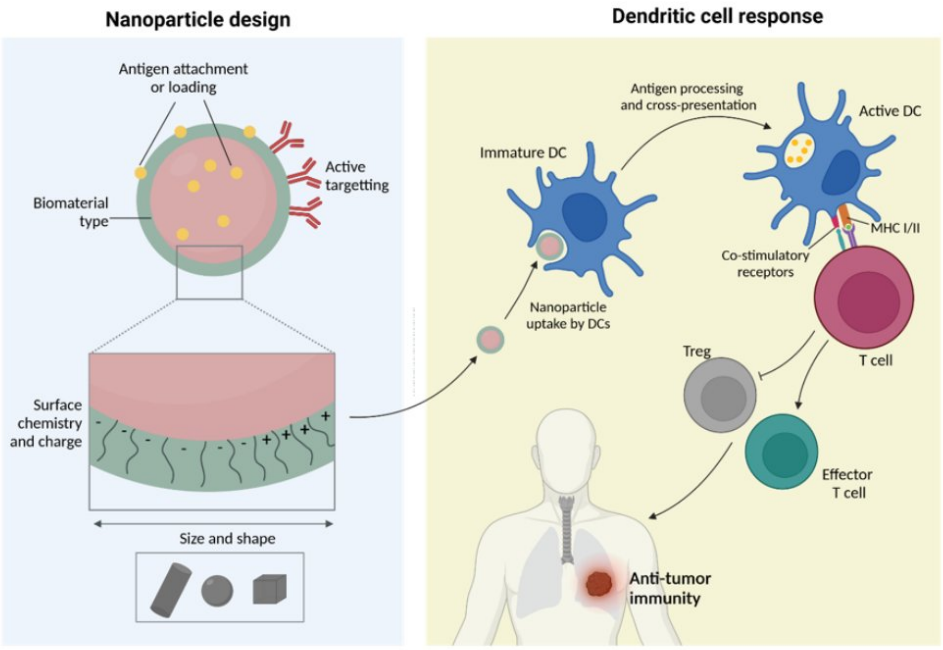
Remarkable breakthroughs have been achieved in the field and this has led to a shift of paradigm in the standard of care from traditional unspecific therapies such a chemo- and radiotherapy, to combined treatment with immunotherapy. Different approaches can be used, but they all have in common the focus in exploiting the host immune system to clear disease. CAR-T cell therapy for example, has led to unprecedent success in inducing cancer remission and even curing B cell malignancy patients, while the discovery of immune

checkpoint blocking has also been a game changer, resulting in higher overall survival of patients with different types of solid tumors [3].
The quest for novel and more effective immunotherapies shows no signs of slowing down with 4720 drugs in the development pipeline this year, corresponding to an increase of 68% since 2017 [4].

Nonetheless, despite the significant improvement in many patients lives, immunotherapy success still often falls short in the long term, not working ubiquitously for all patients. The underachievement of these therapies is related with many factors such as immune composition of the tumor microenvironment, mutational burden of the disease, individual variability, and the side effects that immunotherapies can elicit.

The potential of vaccines and nanomedicine in developing efficient anti-tumor therapies

Compelling data in recent years has led to consensus in the scientific community that potent anti-tumor responses are dependent on successful activation activation of antigen presenting cells and consequent priming of T cells. This solid rational allied with the convincing pre-clinical results is giving rise to great expectations for the of dendritic cell-based vaccination in the near future. However, this has proved to be a not so straightforward path, and there are many hurdles to be overcome such as technical limitations, limited cell availability and lack of methods that allow mapping the immune cell composition in the tumor microenvironment over time following treatment, to name a few.



Nanovaccine design and dendritic cell response. Image adapted from Cifuentes-Rius, A et al, 2021 and created with Biorender.

Nanomedicine might play a key role in addressing some of these hindrances, pushing towards the development of an efficient novel anti-tumor vaccine in the upcoming decades. We have learnt with COVID-19 that nanoparticles can efficiently be used to deliver cargo to cells while simultaneously acting as adjuvant. Besides, they allow the control of several pharmacodynamic parameters, such as half-life of loaded antigens and biodistribution, targeted delivery and even stimulus-dependent release. Thus, fine-tuning of nanoparticles properties can be the key for optimal formulation of novel nanovaccines that modulate immune response.
Within DIRNANO we are actively pursuing this by working in the development of stealth nanoparticles for anti-tumor nanovaccine application and testing them in human immune cells *in vitro* as well as in *in vivo* models.

Establishing an in vitro platform of human DCs for proof-of-concept testing of novel nano-based formulations

In the Horejs-Höeck lab, there is great expertise in handling and characterizing different subsets of human immune cells that are isolated directly from buffy coats of healthy donors.
Within the DIRNANO framework, we are particularly interested dendritic cells as these cells are known to be extremely specialized in sampling tissues for pathogens and they are not only crucial in inducing a quick innate immune response, by secreting a plethora of soluble mediators, but also in mediating the activation of adaptive immunity being essential players in anti-tumor immune responses. Thus, my project is focused in establishing an *in vitro* model of human dendritic cells that mimic the phenotype observed in the tumor microenvironment. This platform can be applied adapted and applied for different cancer types, thus being a relevant model to test nanoparticles designed by other ESRs within the consortium.

DIRNANO NEWS

September marked the beginning of the secondment for a few early-stage researchers (ESRs):

Marek Feith (ESR12) is currently in Salzburg in Horejs-Hoeck group to be trained in the isolation and phenotypical characterization of human immune cells.
Foivos Lazaris (ESR14) and Tom Raju (ESR06) have also travelled to Verona where they will be working in the group of Dr.Roberto Fiammengo in formulating and characterising nanoparticles conjugated with different

biomolecules.
Cristina Cuenca (ESR03) is currently in Newcastle in the group of Dr.Moghimi working in modulation of complement activation.

Regarding participation in conferences and symposiums, Rita Ribeiro (ESR08) has been selected to give a short talk about her project in the annual meeting of Austrian Association of Molecular Life Sciences and Biotechnology in Vienna and she is also taking part in the European's Researchers Night later this month.
Ander Bilbao (ESR09) has also been selected to give a talk about his project in the 2022 Swiss Summer School on Chemical Biology.
Carlos Regaña (ESR05) has attended the International Symposium on Ionic Polymerization in Ghent where he presented a poster displaying his latest data.

All DIRNANO team is also meeting this month in Newcastle (UK) to attend the 2nd Regular Meeting.

Stay tuned and follow all updates in our website and in our LinkedIn page!

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