Updating Precision: Ethical and Societal Aspects of Precision Medicine in the Era of Big Data

RE-IMAGINING 'PRECISION'

The case of cancer immunotherapies

Dr. Luca Chiapperino
SNSF Ambizione Lecturer
STSLab, University of Lausanne
Email: Luca.Chiapperino@unil.ch

Paper in collaboration with Dr. Nils Graber and Prof. Francesco Panese

*an “amalgam” of material, epistemic, social, institutional and political arrangements of science that “in a given field make *how we know what we know*” (Knorr-Cetina 1999:1)

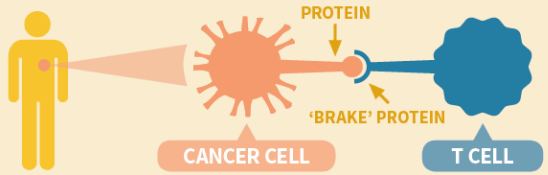
The epistemic culture* of GENOMIC ‘precision’

1) The «hallmarks» of cancer are not just «holistic clarity of mechanism», but therapeutic program (Hanahan and Weinberg, 2000, p.67)
2) Clonal conceptions of cancer have been largely dominant (Marcum 2005; Bertolaso 2011)
3) Experimental care: analytical capability to investigate tumour genomic features with capacity to act on them (Nelson et al. 2013, 2014)
4) A new social contract of medicine? Beyond empowerment lie moral tensions (Prainsack 2017) and pathfinding (Dam et al. 2022)

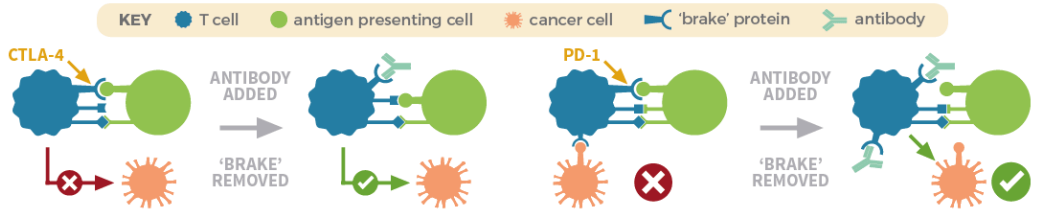
Image Source

2018 NOBEL PRIZE IN PHYSIOLOGY/MEDICINE

The Nobel Prize in Physiology or Medicine 2018 was awarded to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by stimulating the immune system to attack tumour cells.



Cancer is a group of diseases, caused by uncontrolled cell growth, which can evade our immune systems. Proteins on T cells, a type of white blood cell, act as 'brakes' for the immune response. Unleashing these brakes allows the immune system to attack cancer cells.



Allison studied the T cell brake protein CTLA-4. He developed an antibody that could bind to CTLA-4 and block its function, allowing the immune system to attack cancer cells. The antibodies successfully cured mice with cancer, and later human trials were also successful.

Honjo discovered another brake protein, PD-1. It operates by a different mechanism, but also arrests the immune response. Treatment with antibodies releases the brake. This has been effective against different cancers, including metastatic cancer, previously considered untreatable.

WHY DOES THIS RESEARCH MATTER?

This research established an entirely new approach to treating cancer. Positive results have been observed in cancer patients and there are a large number of clinical trials underway against many cancer types.

Nobel Prize in Physiology or Medicine Press release: https://www.nobelprize.org/uploads/2018/10/press-medicine2018.pdf

Today’s talk

Does a a distinct epistemic culture of immuno-genomic precision emerges from the ‘New Cancer Research Center’ (NCRC) in Western Switzerland?

1. Theoretical and experimental hybridizations: opportunities and challenges
2. How do these therapeutic innovations compete with, are enabled by, or get articulated with genomic ‘precision’?
3. What are the epistemic, but also social, political or even economic implications of re-imagining precision in the NCRC?

The Atrium connecting the NCRC (left) and the old pathology building of the Hospital (right).

Courtesy of Baenisch Architekten

An aerial view of the NCRC with the University Hospital in the background.

Courtesy of Baenisch Architekten

Materials and Methods

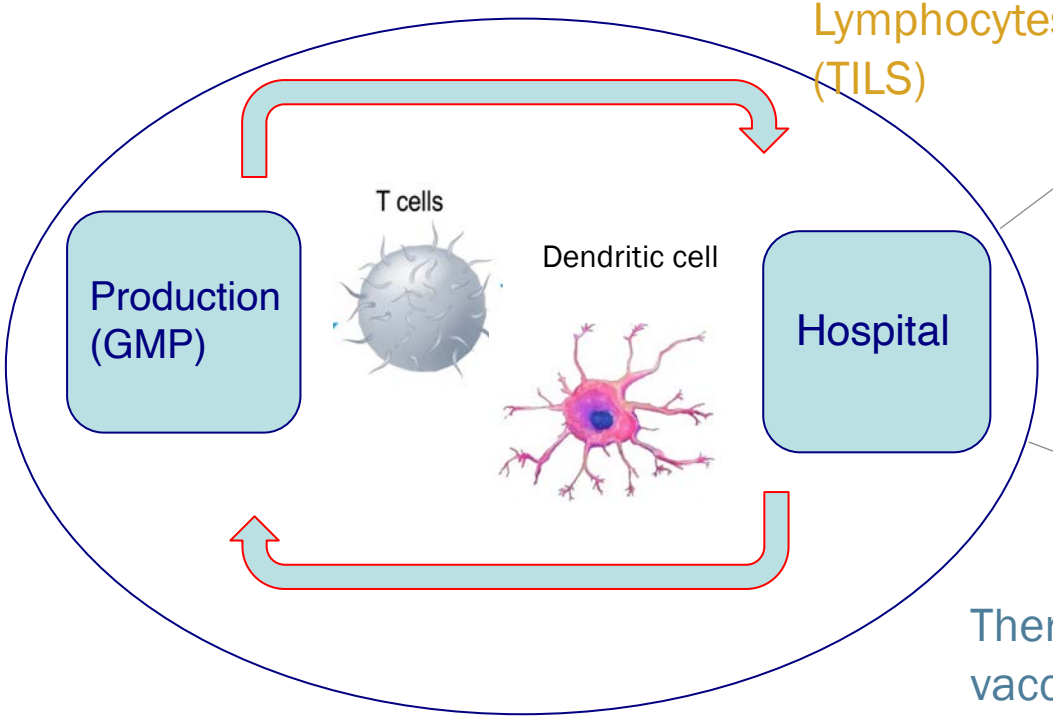
- Interviews (N=16) conducted between 2019 and 2021
- Documents and publications highlighting the strategic role of the NCRC for translational research on cancer immunotherapies.
- Observations of Molecular Tumour Board (NG)

Chiapperino, Luca, Nils Graber, and Francesco Panese. 'Epistemic Dwelling: Precision Immuno-Oncology by Design'. *New Genetics and Society*, 13 December 2020, 1–16. https://doi.org/10.1080/14636778.2020.1853511.

TRANSLATIONAL PIPELINES IN THE NCRC
Developing autologous cell therapies as a new form of ‘precision’ oncology

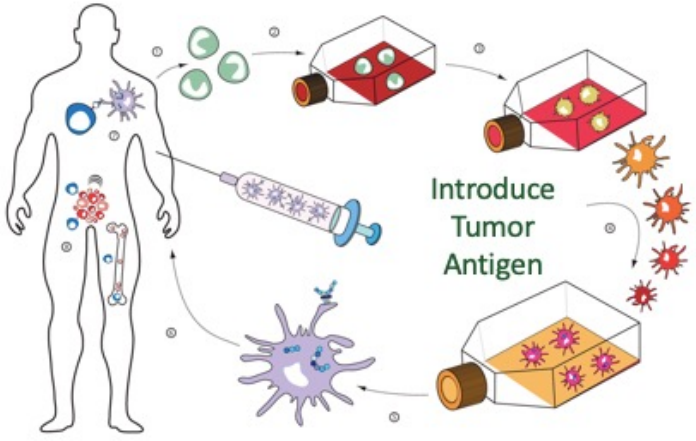
Adoptive cell transfer as personalized immunotherapy for human cancer

Steven A. Rosenberg* and Nicholas P. Restifo*



Adoptive cell therapy using Tumor Infiltrating Lymphocytes (TILS)

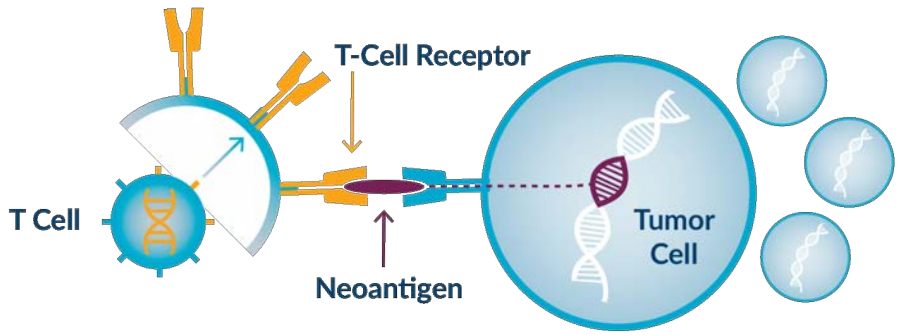
Therapeutic vaccination



Modified slide from Nils Graber

Image source

What are neoantigens?



T-Cell receptors
T-cell receptors or TCRs are molecules on the surface of cancer fighting T cells that have the ability to interrogate individual cancer cells and see beneath the cell membrane.

Neoantigens
Antigens are the unique molecules or proteins that help immune cells identify and fight cancer cells. Neoantigens are unique to each patient's tumor cells.

TCRs have the potential to be genetically modified so T cells can identify the neoantigen signature unique to one patient's cancer cells and then attack them.

RESEARCH ARTICLE

Cancer regression in patients with metastatic melanoma after the transfer of autologous antitumor lymphocytes

Steven A. Rosenberg and Mark E. Dudley Authors Info & Affiliations

October 5, 2004 | 101 (suppl_2) 14639-14645 | https://doi.org/10.1073/pnas.0405730101

Complete regression of melanoma patient after infusion of product with high proportion of neoantigen reactive T cells

Article | March 01 1996

A mutated beta-catenin gene encodes a melanoma-specific antigen recognized by tumor infiltrating lymphocytes.

P F Robbins, M El-Gamil, Y F Li, Y Kawakami, D Loftus, E Appella, S A Rosenberg

+ Author and Article Information

Check for updates

J Exp Med (1996) 183 (3): 1185–1192. https://doi.org/10.1084/jem.183.3.1185

Neoantigens derived from somatic mutations identified in various tumours including melanoma

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2274-2278, April 1988
Immunology

Immunogenic (tum⁻) variants of mouse tumor P815: Cloning of the gene of tum⁻ antigen P91A and identification of the tum⁻ mutation*

(tumor immunology/cosmid/mastocytoma P815)

ETIENNE DE PLAEN, CHRISTOPHE LURQUIN, ALINE VAN PEL, BERNARD MARIAMÉ, JEAN-PIERRE SZIKORA, THOMAS WÖLFEL, CATHERINE SIBILLE, PATRICK CHOMEZ, AND THIERRY BOON

Ludwig Institute for Cancer Research, Brussels Branch, 74 avenue Hippocrate, B-1200 Brussels, Belgium

Communicated by C. de Duve, December 9, 1987 (received for review October 12, 1987)

Study reporting antitumour T cells can recognize peptides derived from tumour-specific mutations

Theoretical hybridization:

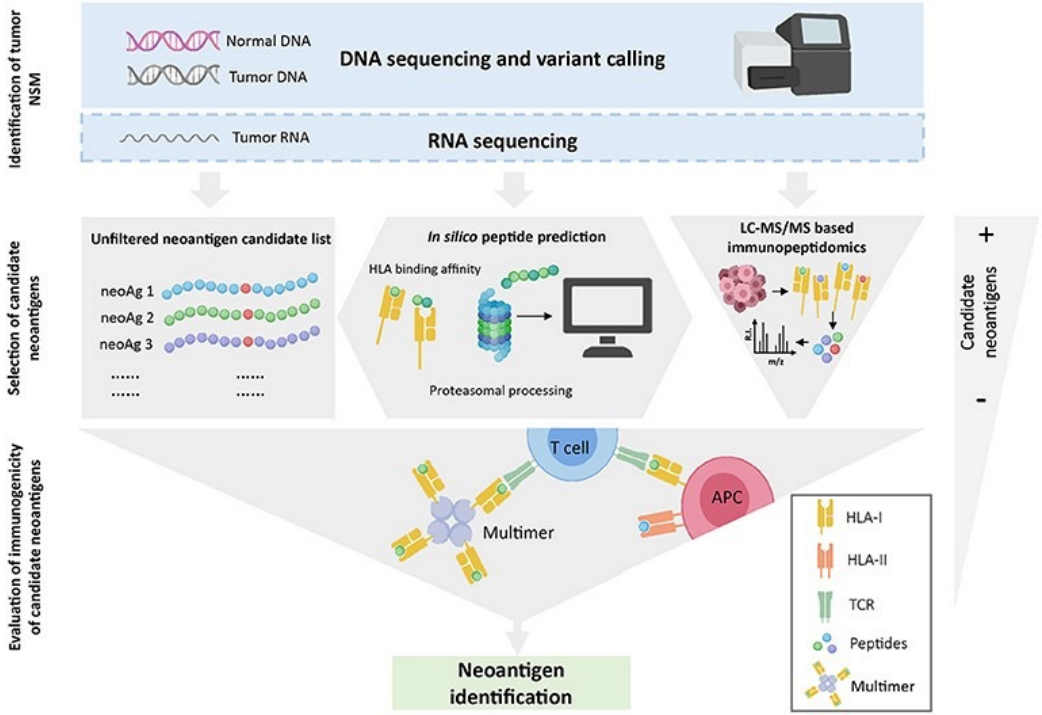
A different and yet fully integrated therapeutic project?

*"[The first ACTs we developed were already] **personalized** because it's the autologous tumour, but now comes the fancy definition of **private** neoantigens. […] Private, because the likelihood to find the same mutation in two patients is very unlikely, right? These mutations occur stochastically so your genome is three billion base pairs and any of this is mutated […] We developed a way to [characterize the impact of mutations on the cancer cells' antigens] so that at the end you have a therapeutic product […] more tumour reactive and theoretically more efficient."*

(Immunologist Group Leader; emphasis added)

How to identify neoantigens in tumour cells?

"Back in the 1990s we vaguely knew about the importance of neoantigens, but we lacked the analytic tools to identify them. Now, in the blink of an eye, we get the genome of a cancer" (Clinician-Researcher)



Step 1: Identification of tumor non-synonymous mutations (NSM). Exome sequencing is performed on tumor and normal DNA to identify tumor-specific NSM. When available, RNA-seq is used to select mutations that are expressed.

Step 2: Selection of candidate neoantigens. Once NSMs are identified, three strategies can be used to select the list of candidate neoantigens that will be assessed for immunogenicity (e.g. prediction and MS).

Step 3: Evaluation of immunogenicity of candidate neoantigens. Finally, the immunogenicity of the selected candidate peptides is evaluated with different immunological screening assays (e.g. FACS).

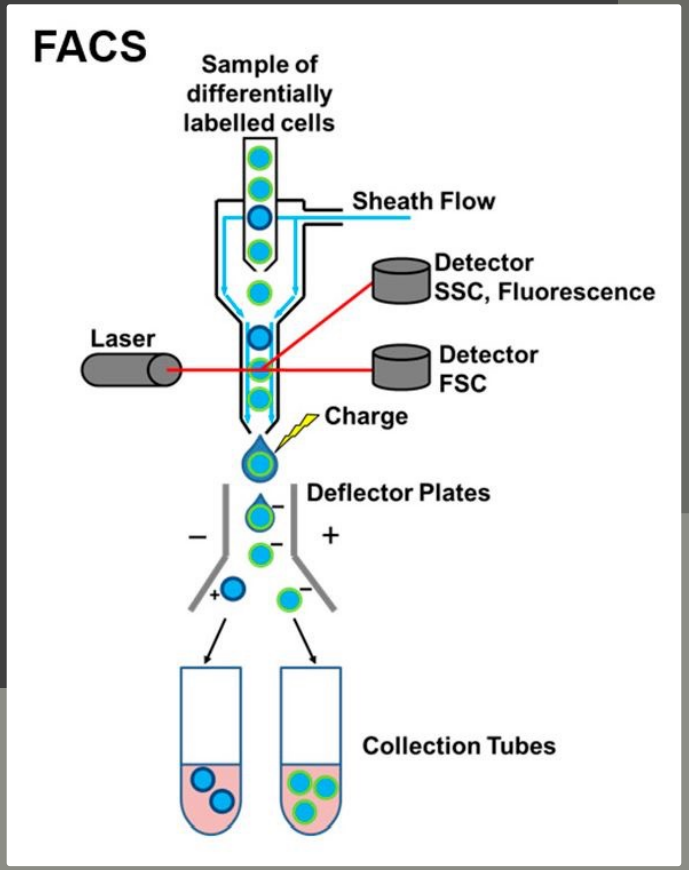
Adapted from Garcia-Garijo et al. 2019

Experimental hybridization:

Stabilising ‘neoantigens’ by connecting experimental systems

“Neoantigens are… you have to prove them, you have to validate; some exist, but everything starts from mass [spectrometry] data or prediction. […] My main concern is everything relies on bioinformatic analysis that are currently being developed and we are not sure that we are reaching for the right neoantigens. So, if the prediction is wrong, finally you could end up with a population enriched in neoantigens that you inject into the patient, but that are not the good antigens.”

(Translational researcher; emphasis added)



CONCLUSIONS

1. Neoantigens redefine and challenge how we know, experiment with and treat cancer
   - ⇢ *To what extent ought 'precision' to be still defined, practiced, and known through the dominant tools and concepts of genomics?*
2. The clinical translations of neoantigens-based ACT require a hybrid biomedical platform
   - ⇢ *How does one bring this view of 'precision' to real-world clinical settings?*
3. Does re-imagining precision mean also renegotiating socio-political configurations of biomedicine?
   - ⇢ *From an economy of products (e.g. targeted drugs) to process and infrastructure (e.g. vein-to-vein circuit of cell product manufacturing)*
   - ⇢ *What are the ethical, economic, political challenges of 100k.- 'precision' therapeutics?*

Nils Graber

Franco Panese

THANKS FOR YOUR ATTENTION

Luca.Chiapperino@unil.ch

If you are interested in knowing more about this research:

- Chiapperino L., Graber N., Panese F. Under Review. “Navigating uncertainties in the making of precision immuno-oncology: the case of neoantigens-based cellular therapies”.
- ––––. Forthcoming. “Explanatory pluralism in oncology. The case of adoptive cell transfer immunotherapies”. Hens K. and de Block, A. (eds.), Advances in Experimental Philosophy, Bloomsbury
- ––––. 2020. “Epistemic dwelling: precision immuno-oncology by design”, New Genetics and Society. Online first. https://doi.org/10.1080/14636778.2020.1853511.