Novel Pediatric Anti-Cancer Vaccines

From discovery → development → cure

A vision for curing every child

Dr. Aru Narendran
Clinician-Scientist, Pediatric Oncology





Thank you KCC for supporting child-centered research

THE UNMET NEED

We have become better at treating childhood cancer — but not equally successful at curing certain ones

Some with no advancements in over 20 years !

What we have	What remains	What we need
• Chemotherapy • Surgery • Radiation • Transplant / other therapies	• Relapsed disease • Metastatic disease • Treatment toxicity • Limited salvage options	• New mechanisms • Precision therapies • Durable tumor-specific immunity • Therapies designed around tumor biology

The next generation of pediatric cancer therapy must be biologically precise — not simply more intensive.

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"Can we make the immune system part of the treatment?"

Possible mechanisms for relapse

Likely complex and multifactorial

The problem:

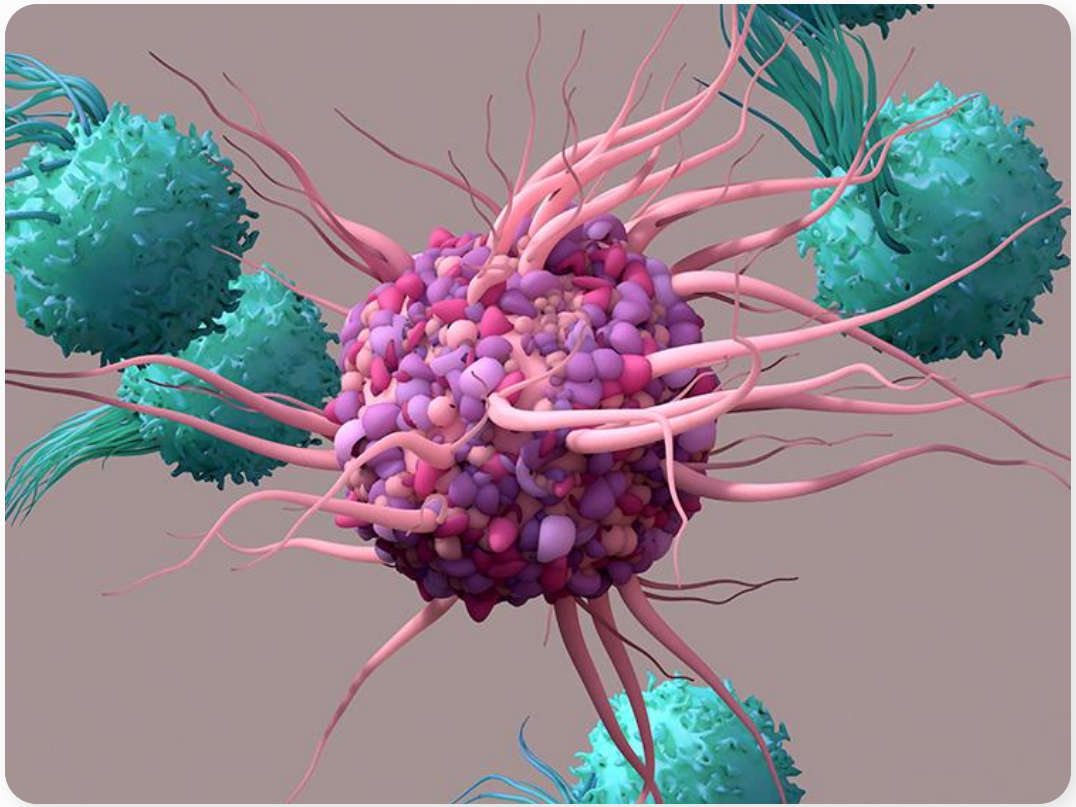
Immune cells don’t recognize the tumor as something that shouldn’t be there

The Solution: Then educate them –

Bring back immune recognition and activation to kill the cancer cells

Neoantigen vaccines

Why this matters for pediatric cancers



- **Prevent Relapse:** Clears resistant cells hiding from chemo.
- **Precision:** Targets cancer specifically, sparing healthy growing tissue.
- **Fewer Side Effects:** Smart combinations could reduce toxic late effects.

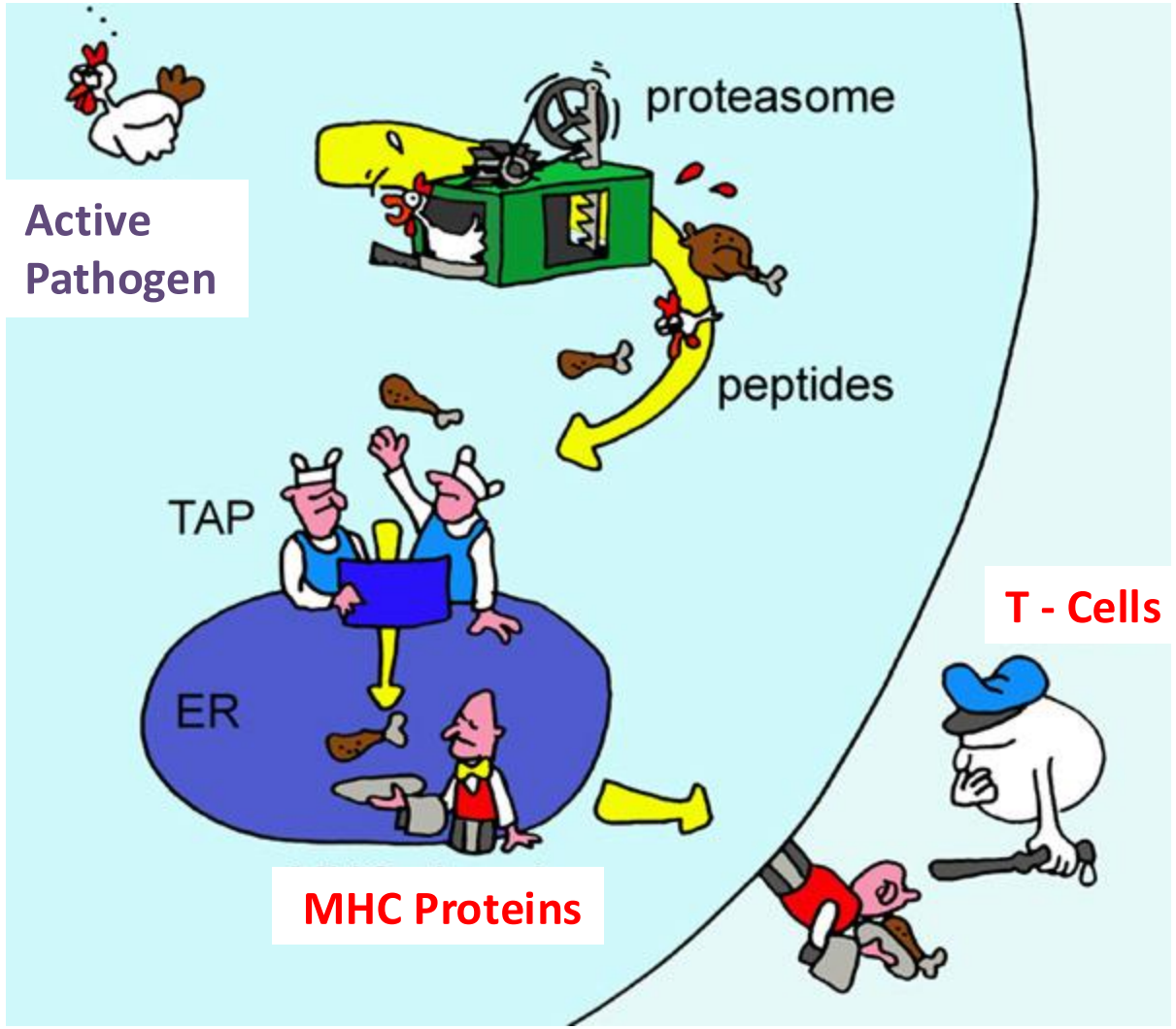
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What is a neoantigen vaccine?



General immune activation process*

INFECTION

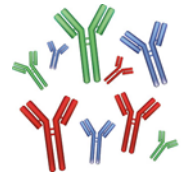


Cytotoxicity of infected cells

Elimination of the pathogen

Immune Memory

Activation of corresponding B-Cells



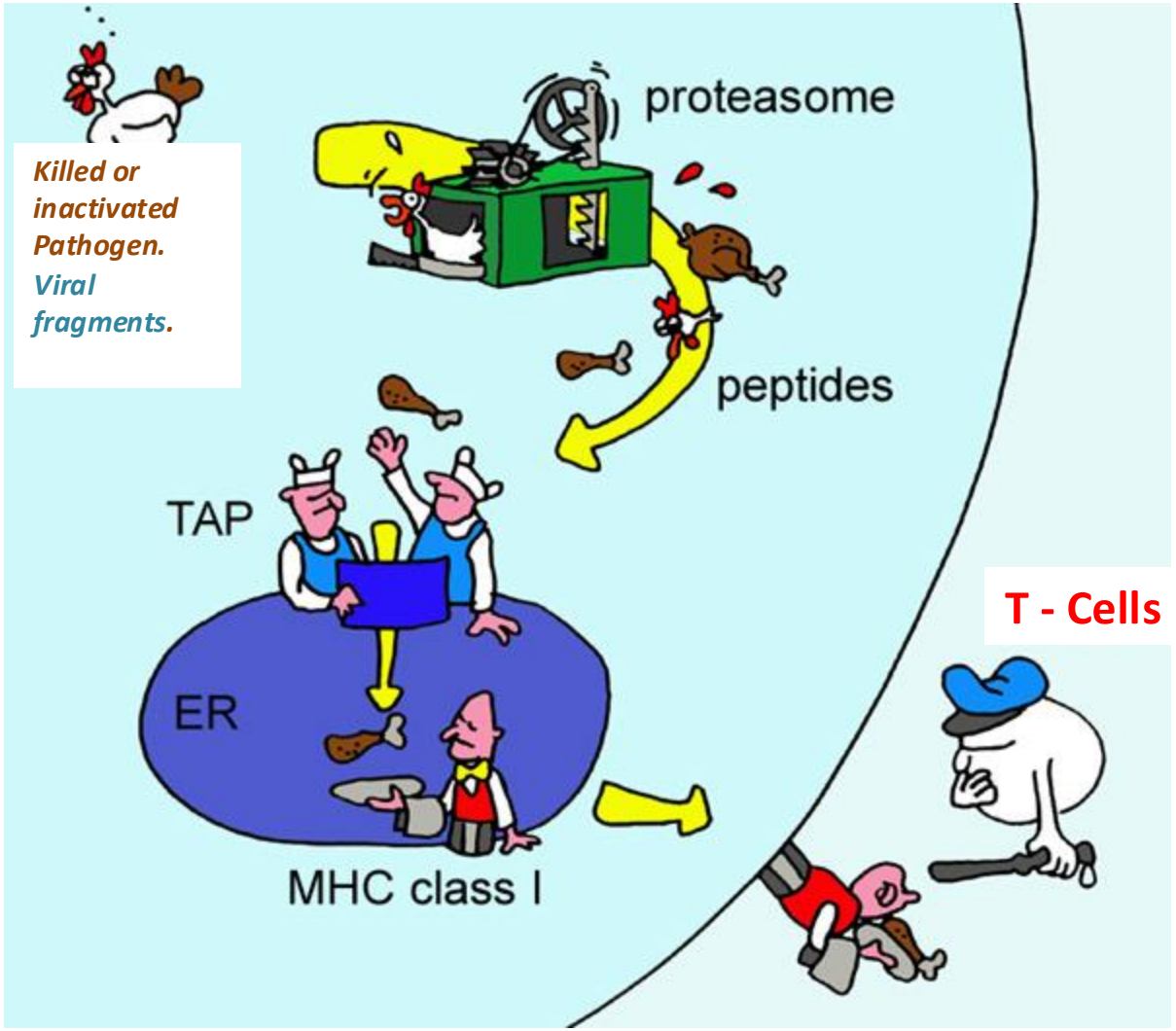
Anti-pathogen antibodies

Yewdell et al. Nature Reviews Immunology. 2003

Immune activation after vaccines



Immunization



Immune Memory

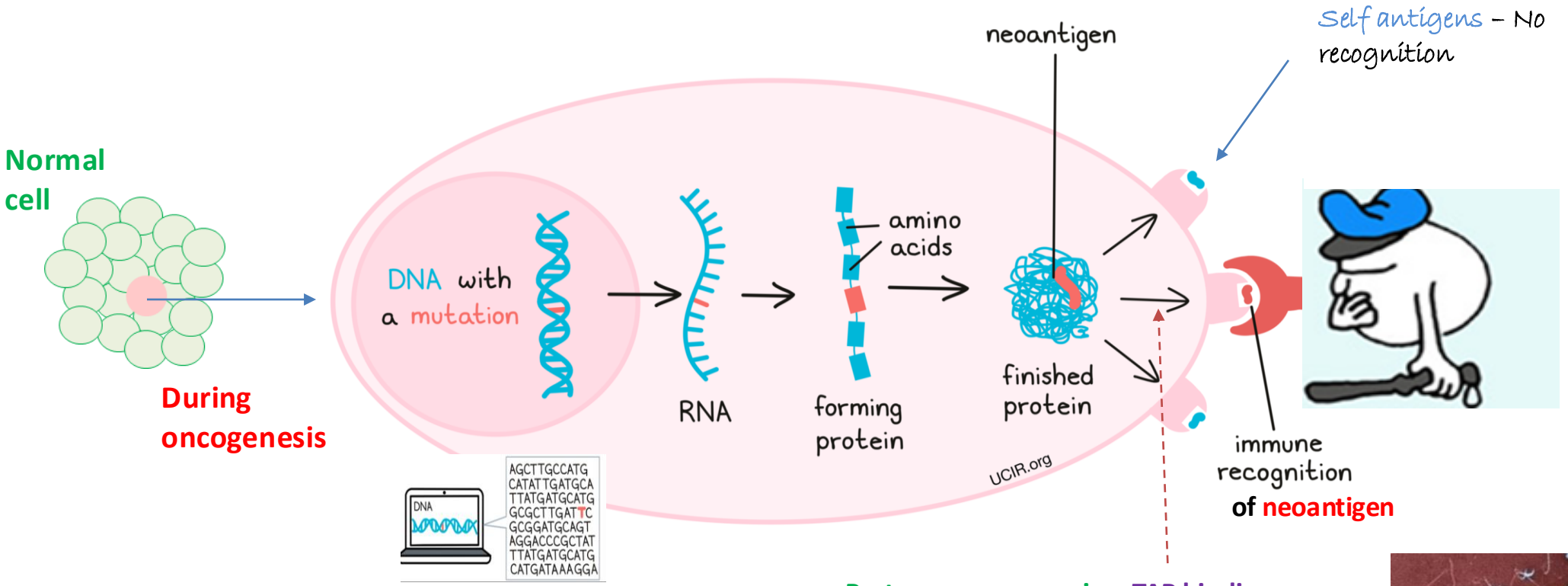
Activation of corresponding B-Cells



Anti-pathogen antibodies

Yewdell et al. Nature Reviews Immunology. 2003

When a normal cell becomes a cancer cell…



Proteasome processing, TAP binding and MHC binding



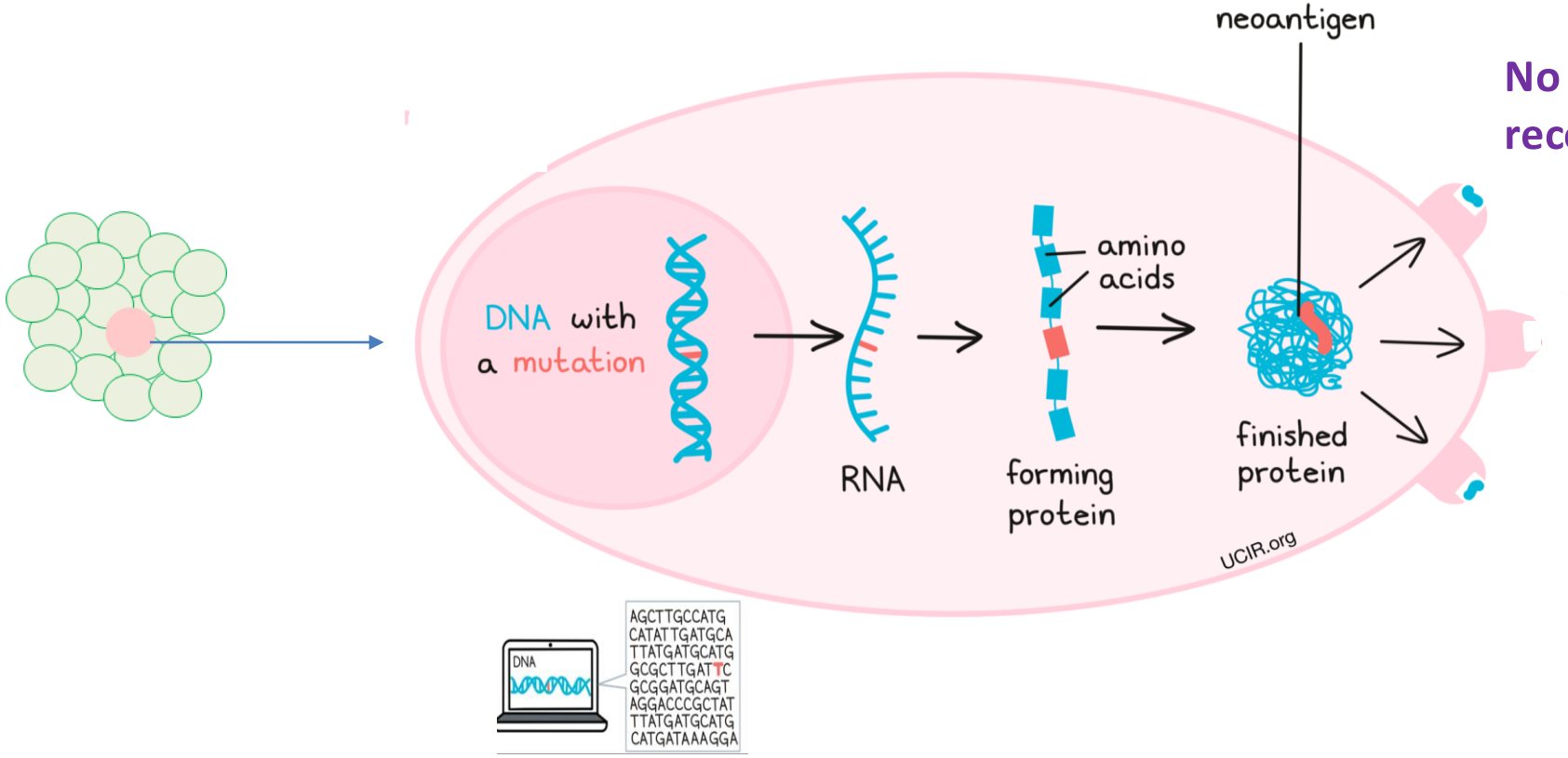
Neoantigens are generated
Through a variety of mutational events
Include point mutations,
insertions or deletions and gene fusions
In tumours driven by viruses, viral proteins - foreign nature

https://www.neogene.com/ourscience/

Cancer cell growth

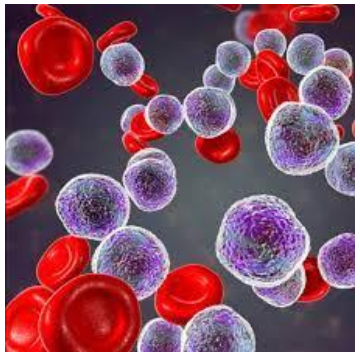
No effective Neoantigen presentation and

No Immune recognition





T - Cells



The Plan: Provide functionable neoantigens as a vaccine to bring back immune recognition and activation

https://www.neogene.com/ourscience/

Recently a number of studies have shown encouraging evidence for neoantigen vaccines to activate the IS against cancer

Aurisicchio *et al. Journal of Experimental & Clinical Cancer Research* (2018) 37:86
https://doi.org/10.1186/s13046-018-0751-1

Journal of Experimental & Clinical Cancer Research

REVIEW Open Access

The perfect personalized cancer therapy: cancer vaccines against neoantigens

Luigi Aurisicchio[1,2*], Matteo Pallocca[3], Gennaro Ciliberto[4] and Fabio Palombo[1,5]

Abstract

In the advent of Immune Checkpoint inhibitors (ICI) and of CAR-T adoptive T-cells, the new frontier in Oncology is Cancer Immunotherapy because of its ability to provide long term clinical benefit in metastatic disease in several solid and liquid tumor types. It is now clear that ICI acts by unmasking preexisting immune responses as well as by inducing de novo responses against tumor neoantigens. Thanks to theprogress made in genomics technologies and the evolution of bioinformatics, neoantigens represent ideal targets, due to their specific expression in cancer tissue and the potential lack of side effects. In this review, we discuss the promise of preclinical and clinical results with mutation-derived neoantigen cancer vaccines (NCVs) along with the current limitations from bioinformatics prediction to manufacturing an effective new therapeutic approach.

Background

capable of targeting a specific genomic alteration. An in-

The Journal of Clinical Investigation RESEARCH ARTICLE

Imaging activated T cells predicts response to cancer vaccines

Israt S. Alam,[1,2] Aaron T. Mayer,[1,2,3] Idit Sagiv-Barfi,[4] Kezheng Wang,[1,5] Ophir Vermesh,[1,2] Debra K. Czerwinski,[4] Emily M. Johnson,[1,2,6] Michelle L. James,[1,2,6] Ronald Levy,[4] and Sanjiv S. Gambhir[1,2]

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LETTER

doi:10.1038/nature22991

An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3*], Zhuting Hu[1*], Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[7], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4†], Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

LETTER

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3*] & Özlem Türeci[8*]



A Novel Anti-cancer Vaccine Approach for the Effective Treatment of Refractory Leukemia in Children

Son Tran[1], Patrick Sipila[1], Chunfen Zhang[1], Luke Maese[2], Norman Lacayo[3], **Aru Narendran[1]**

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[2] University of Utah, Department of Pediatrics, Salt Lake City, UT, United States of America

[3] Stanford University School of Medicine and Stanford Cancer Institute, Department of Pediatrics, Palo Alto, CA, United States of America

How are we prepared:

A pediatric vaccine + checkpoint-blockade trial is already registered and recruiting across these sites. The Clinical Study



Participating Centers

- Lurie Children's Hospital (lead site), Chicago
- Dana Farber Cancer Institute, Boston
- Children's Hospital Orange County (CHOC), LA
- Alberta Children's Hospital, Calgary

Calgary is already an activated site in this study network.

Advantages of peptide-based vaccines

•The absence of infectious material
•Easy purity assessment
•Easy to produce, economical
•Easy storage - freeze dried - no cold chain facility

Drawbacks:
•Adjuvant science, lipopeptide conjugation and direct delivery to dendritic cells

- some of the approaches currently being used to overcome these problems

How KCC accelerates cures

- **Seed Funding:** Launching high-risk, high-reward ideas.
- **Early Trials:** Supporting first-in-child studies & science.
- **Family Support:** Travel & housing to enable participation.

"KCC funds the gap between discovery and first-in-child."



