City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

APPENDICEAL CANCERS

Tackling Recurrence: Peptide Vaccines in the Treatment of PMP

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Disclosures

- Grant/Research Support from Bayer.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or its products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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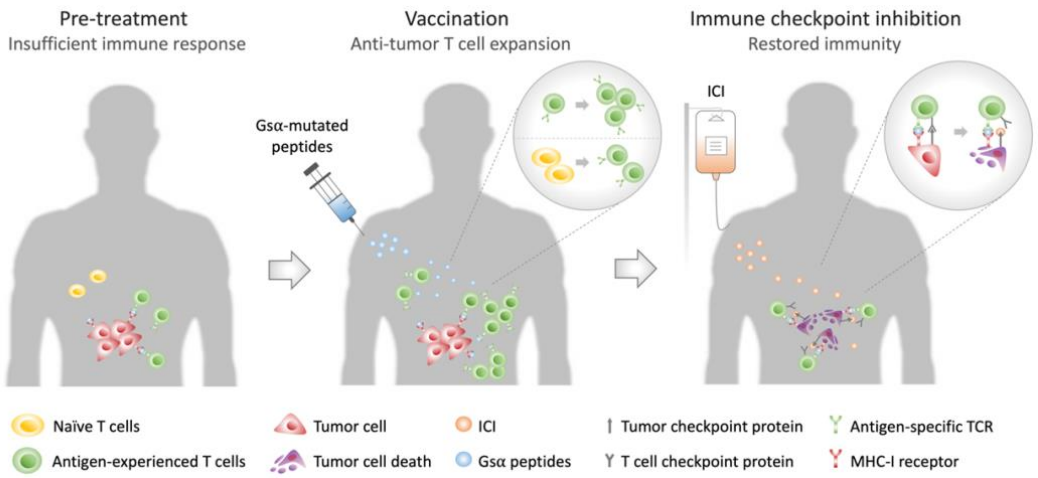
Outline

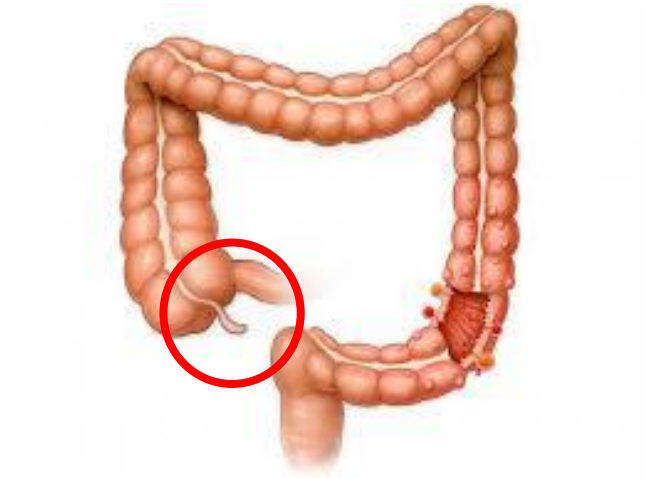
- Pseudomyxoma peritonei – background
- Our research provides rationale for treatment with a peptide vaccine in pseudomyxoma peritonei
- The Pseudovax phase I trial concept

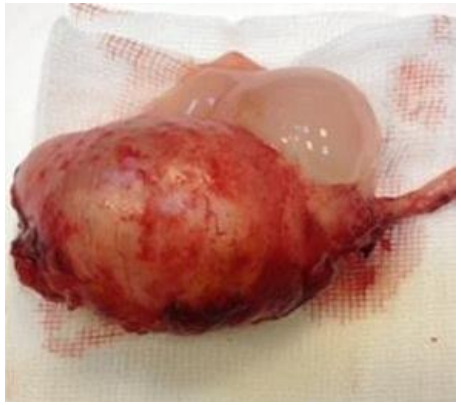


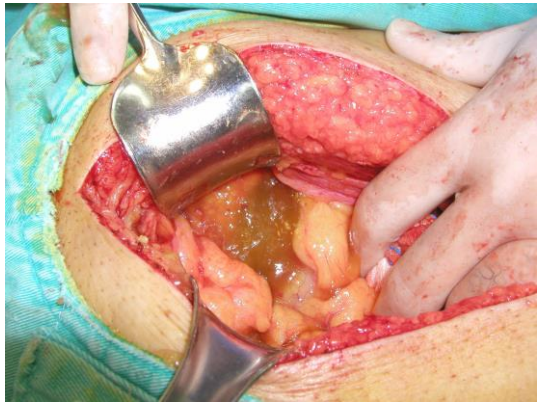
Pseudomyxoma peritonei – a very strange disease

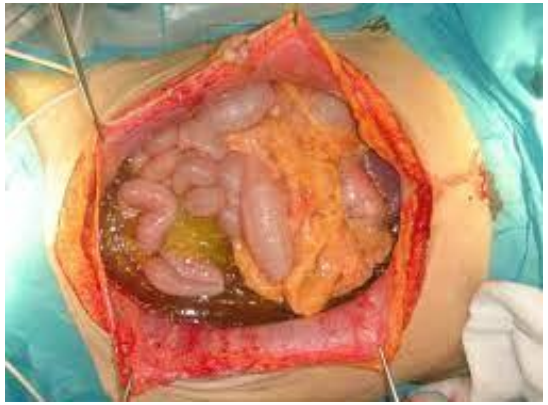
- Rare abdominal cancer, incidence 3.2 persons/million/year

Patrick-Brown, *Ann Surg Oncol*, 2020





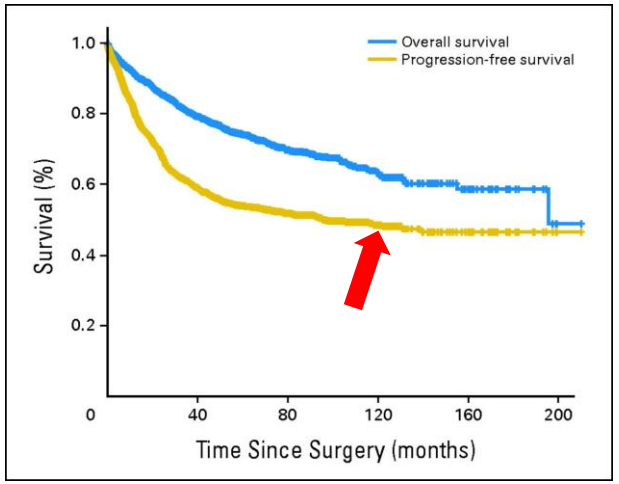




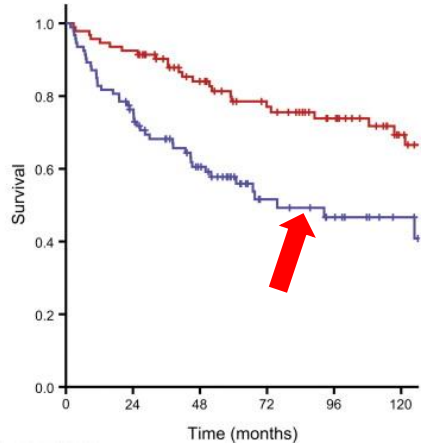
Treatment

- Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC)
- Half of the patients are cured

- BUT for patients with non-resectable and recurrent disease, no good treatment options exist



Chua; *J Clin Oncol*; 2012



Sørensen; *Eur J Surg Oncol*; 2012

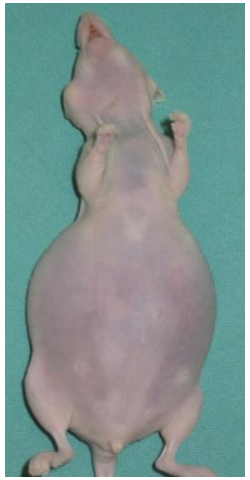
How to approach this research challenge

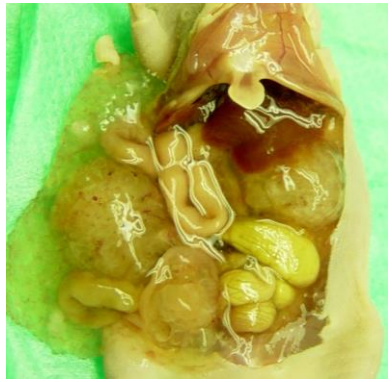
PMP is a rare disease;
we must work together to facilitate progress

EuroPMP cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020
Framework Programme
of the European Union

Experimental models – necessary for development of new drugs and treatment strategies

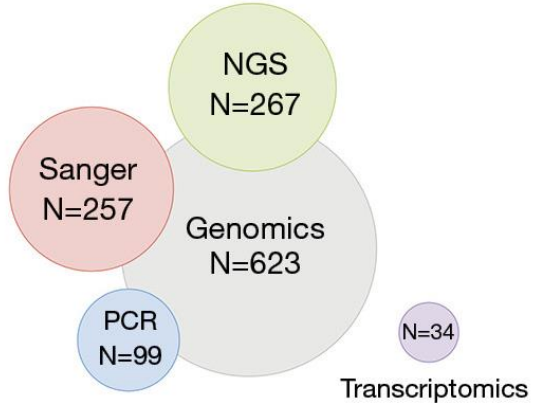




Flatmark et al; *BMC Cancer*; 2007
Flatmark et al; *Hum Pathol*; 2010
Flatmark et al; *Int J Cancer*; 2013
Fleten et al; *Transl Oncol*; *2020*

The molecular basis is incompletely characterized

- Mainly mutation analysis



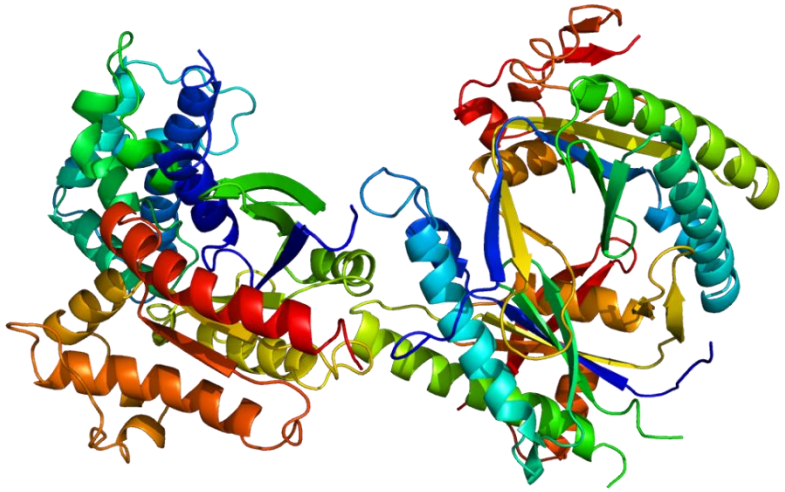
Lund-Andersen et al; *J Gastrointest Oncol*; 2021

- *KRAS* and ***GNAS*** mutations

Mutations in the *GNAS* oncogene are surprisingly frequent in PMP

- *GNAS* encodes guanine nucleotide-binding protein α subunit (Gsα)
- One of the most frequently mutated G-proteins in cancer (4.4%)
- Reported mutation frequency in PMP 60-100%
- Activating mutations in codon 201 (pR201H and pR201C)
- Protein kinase A signalling associated with mucin production

- No successful therapeutic strategies targeting *GNAS*

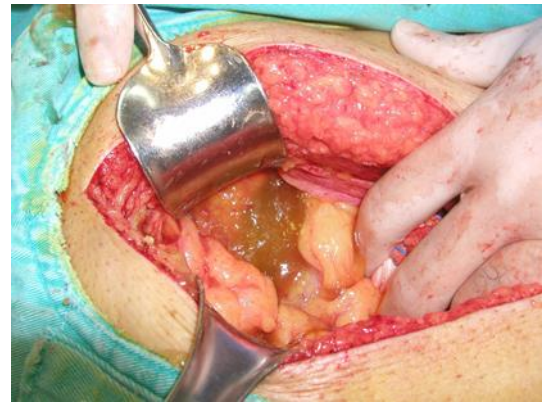


https://commons.wikimedia.org/w/index.php?curid=9444597

Our research – is Gsα a cancer neo-antigen?

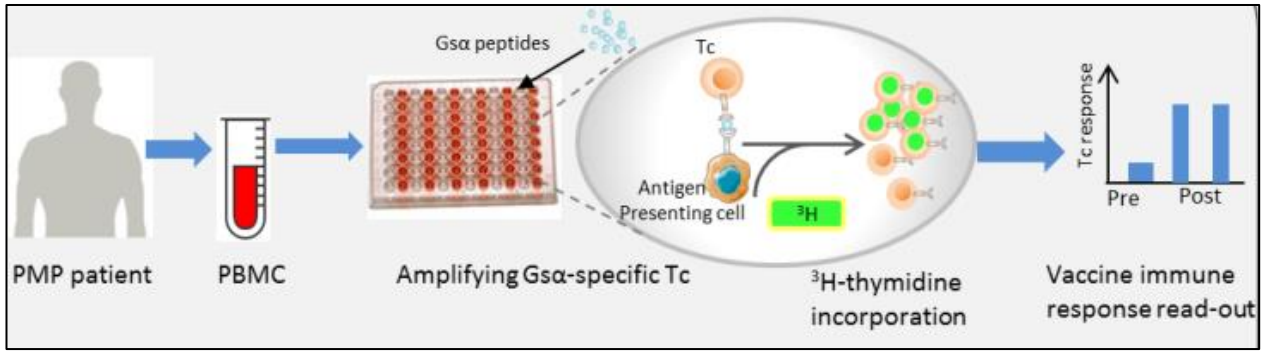
- Peripheral blood samples and tumor tissue from 25 PMP patients undergoing surgery for PMP

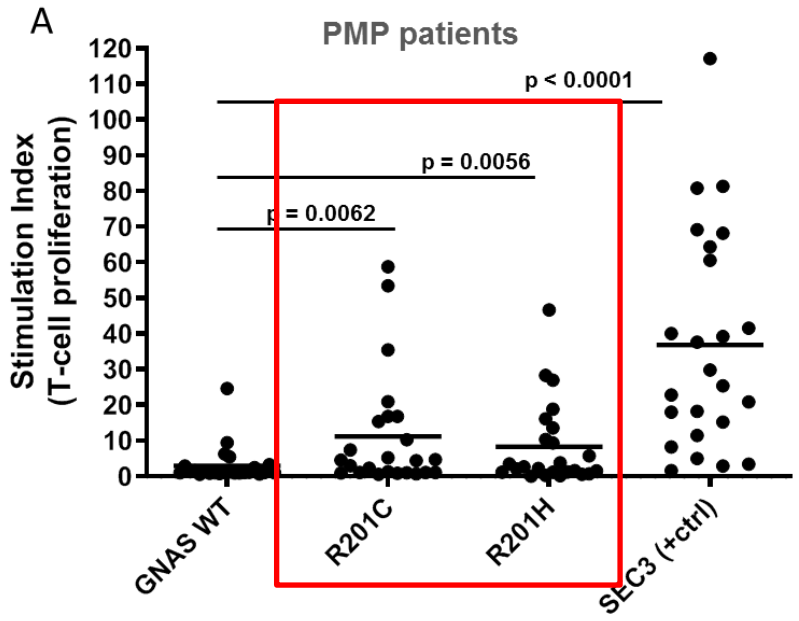
- Mutation analysis (targeted NGS or dd PCR)
  - Mutations detected in 22/25 samples (88%)
  - R201H/R201C – 16/6



Our research – patient T cells respond to mutated Gsα

T cell proliferation assay





There is a pre-existing immune response against mutated Gsα

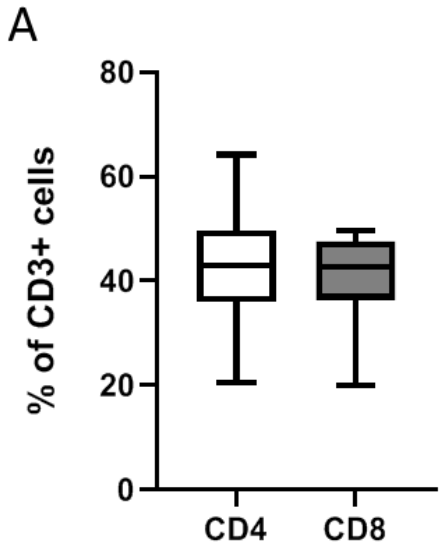
Flatmark and Inderberg et al; *J Immunother Cancer*; 2021

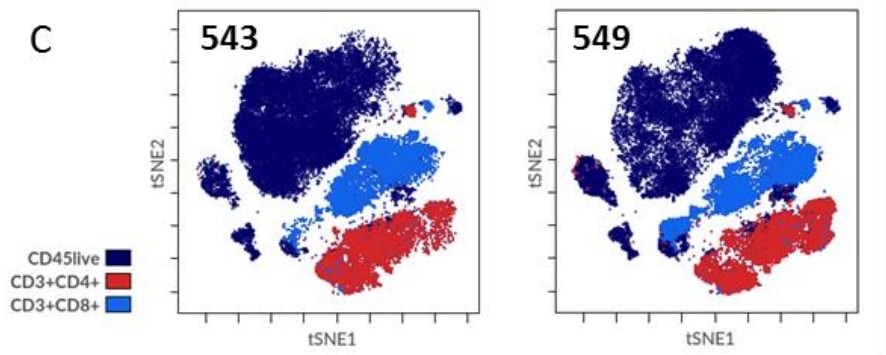
Our research – T cells in PMP tumor samples

If there is an anti-Gsα immune response, why did these patients develop PMP?

No tumor infiltrating T cells?

Quite the opposite!





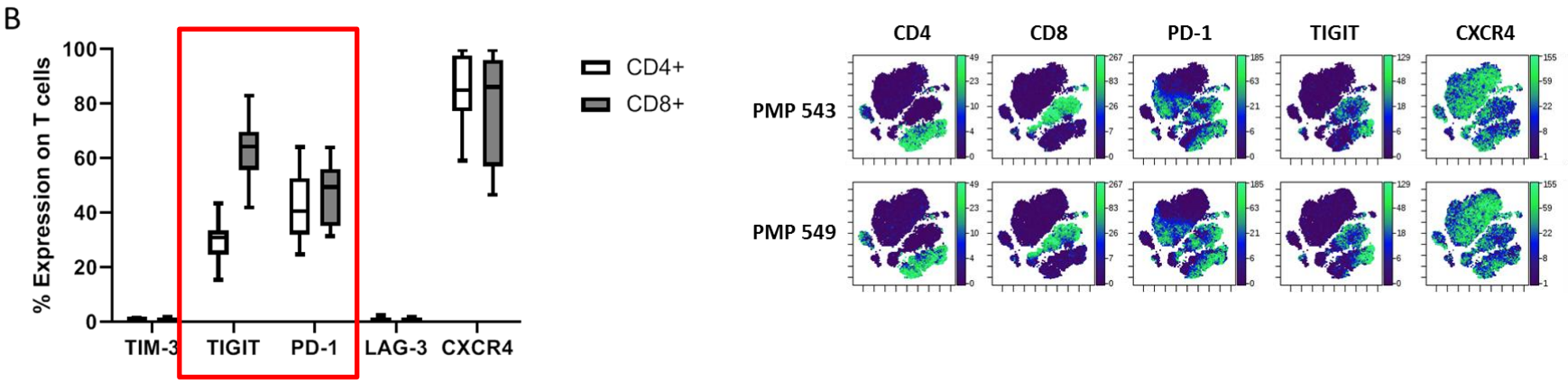
CyTOF analysis

Flatmark and Inderberg et al; *J Immunother Cancer*; 2021

Our research – T cells in PMP tumor samples

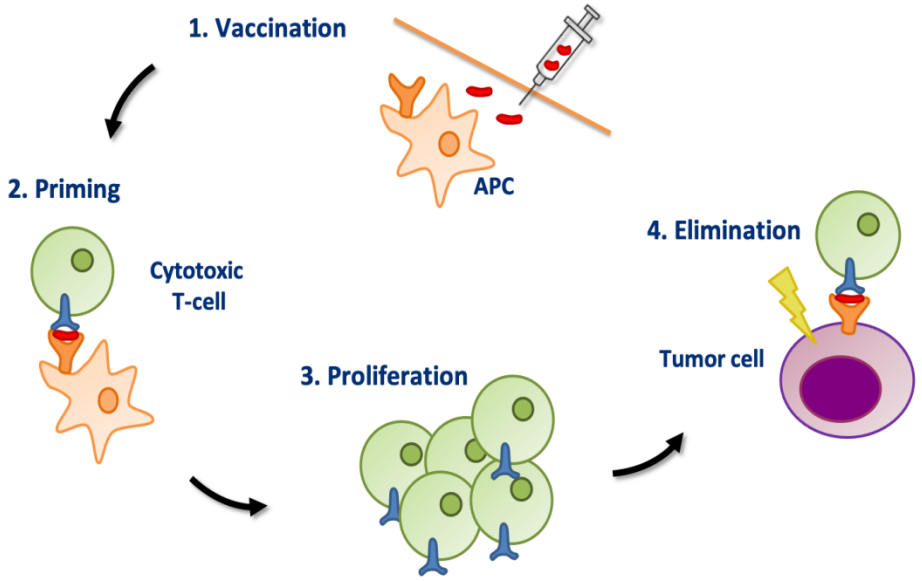
If there is an anti-Gsα immune response, and T cells are able to reach the tumor, why did these patients develop PMP?

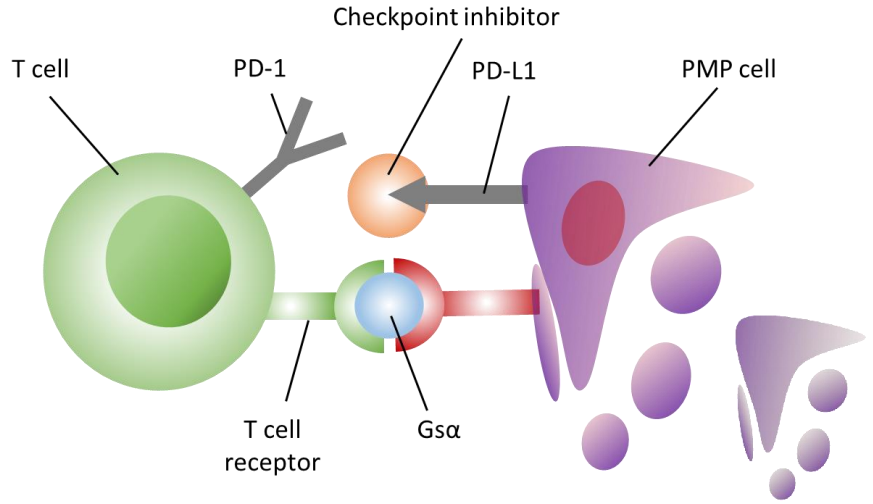
T cells express immune checkpoint molecules



Flatmark and Inderberg et al; *J Immunother Cancer*; 2021

The Pseudovax idea:
Combine a cancer vaccine against mutated *GNAS* with a checkpoint inhibitor





The Pseudovax trial concept

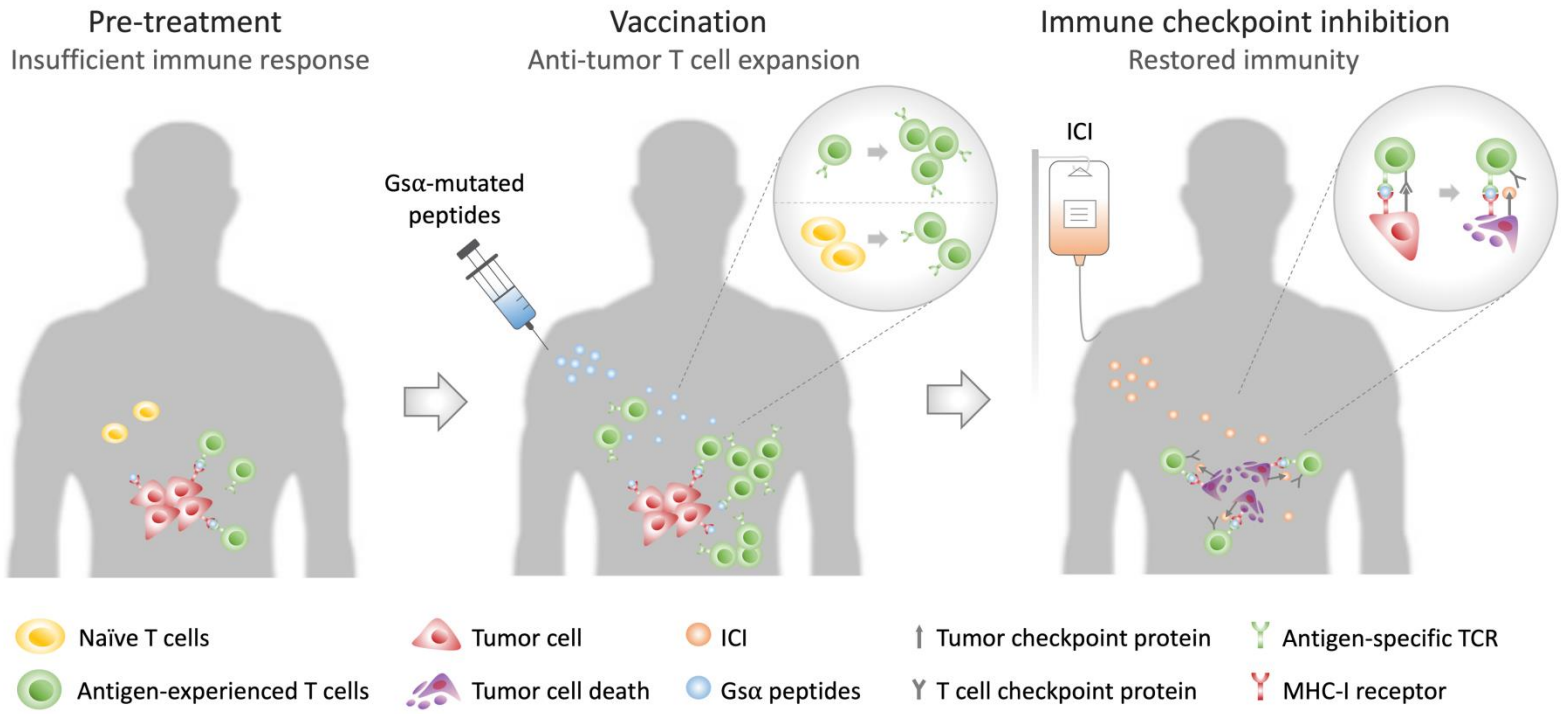
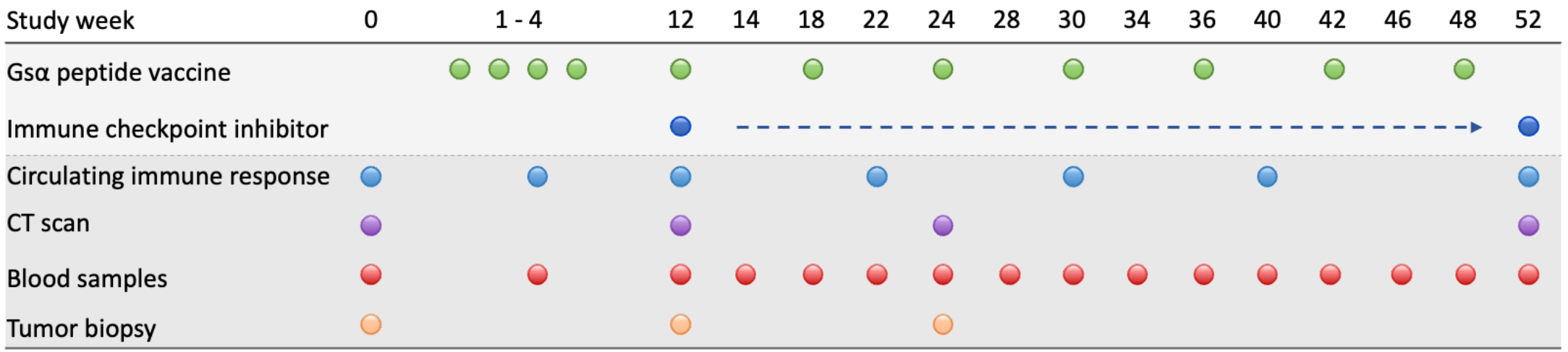


Figure by Christin Lund-Andersen

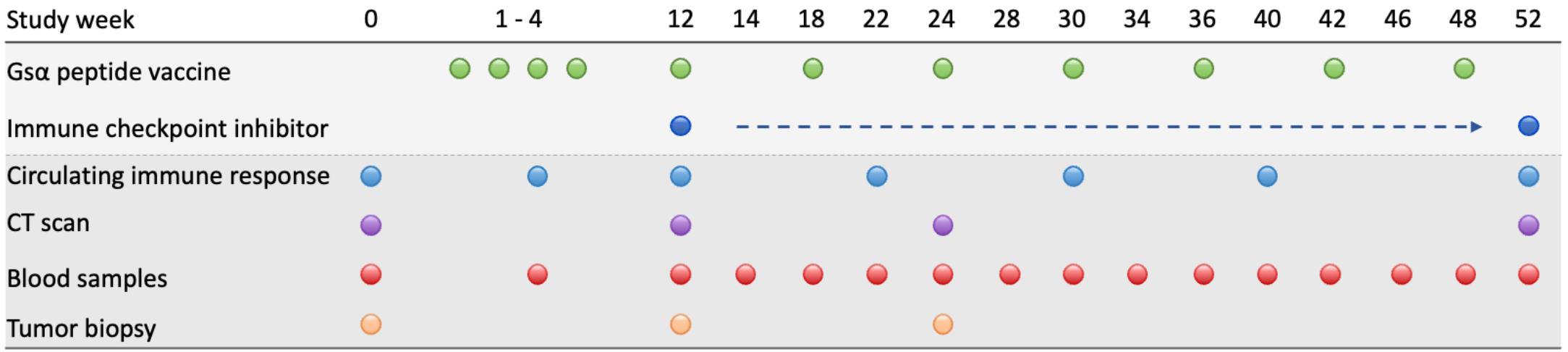
The Pseudovax phase I trial

- «First-in-man»
  - Safety/toxicity
  - Immune responses?
- Small trial ~10 patients



The Pseudovax phase I trial

- Timeline
  - Essential national funding was obtained from the Norwegian Cancer Society in September 2021
  - Non-GMP (technical) batch vaccine production startet June 2022
  - Earliest estimate for trial initiation is January 2024
  - Our main challenge is still funding!
    Very helpful support from patient organizations in Norway, UK charities (Pseudomyxoma survivor and Charities Aid Foundation) and hopefully, ACPMP



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Pathology

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Gastroenterological Surgery

Surgeons

Nurses

Experimental Cancer Therapy

Geir Olav Hjortland

Our PMP patients