ADVANCING INNOVATIVE THERAPIES FOR CANCERS THAT INVADE THE PERITONEUM AND THE PLEURA

Tackling Recurrence: Peptide Vaccines in the Treatment of PMP

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APPENDICEAL CANCERS
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._
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

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

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

The molecular basis is incompletely characterized

- Mainly mutation analysis
  - KRAS and GNAS mutations

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Funded by the Horizon 2020 Framework Programme of the European Union

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

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

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Norwegian Radium Hospital

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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

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 $\textit{GNAS}$ with a checkpoint inhibitor
The Pseudovax trial concept

Pre-treatment
Insufficient immune response

Vaccination
Anti-tumor T cell expansion

Immune checkpoint inhibition
Restored immunity

Figure by Christin Lund-Andersen
The Pseudovax phase I trial

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

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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 started 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
Ben Davidson

Gastroenterological Surgery
Surgeons
Nurses

Experimental Cancer Therapy
Geir Olav Hjortland

Our PMP patients

Translational Cancer Therapy

Cure 4 PMP
Helse Sør-Ost
EuroPMP