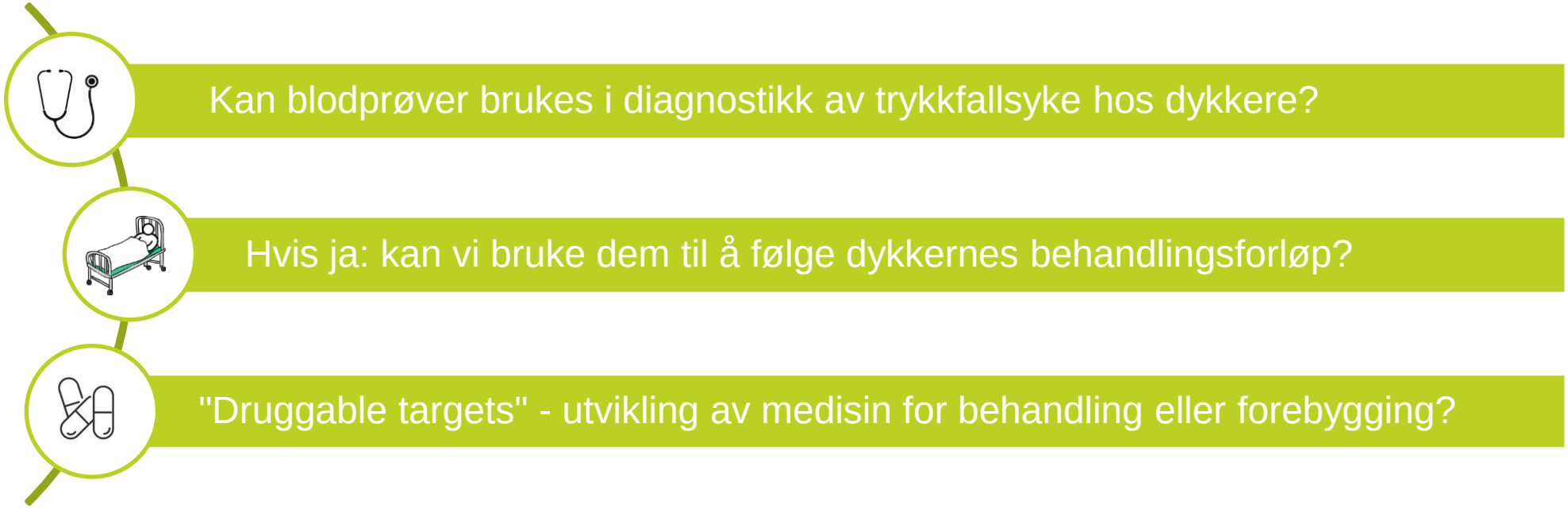
Kan en blodprøve avdekke trykkfallsyke?

Ingrid Eftedal, PhD
NTNU Fakultet for medisin og helsevitenskap

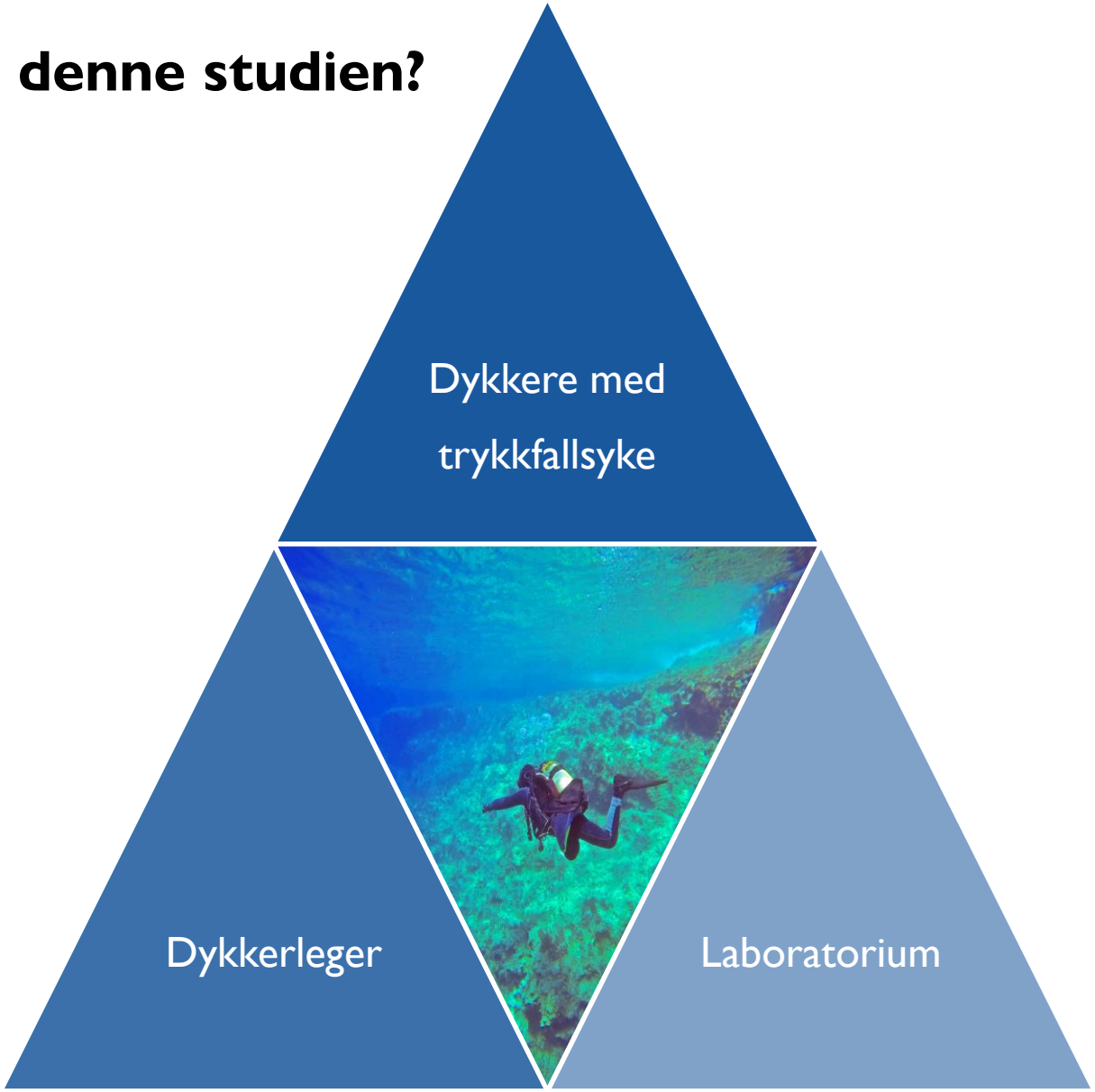
Denne studien bygger på empirisk og vitenskapelig kunnskap samlet inn av mange over mer enn 100 år.

Vi støttet oss også på tidligere studier av immunforsvarets reaksjoner på ekstreme omgivelser, fra NTNU og andre forskningsmiljøer.

Spørsmålene som ligger til grunn for studien



Hva var spesielt med denne studien?



Vrakdykking ved Malta

- Maltas sentrale plassering i Middelhavet: viktig for handel, ofte invadert.
- Skipsvrakene rundt Malta er attraktive for sportsdykkere.
- Hvert år behandler Mater Dei-hopitalet 50-100 syke dykkere.
- De fleste behandlingene skjer i sommersesongen.

Studiedesignet

Etter at studieprotokoll, finansiering, samarbeidsavtaler og etisk godkjenning var på plass, var det bare å vente på syke dykkere

Dykkere med trykkfallsyke ble undersøkt og behandlet med hyperbart oksygen. Blodprøver før (T1) og 48 timer etter (T2) oksygenbehandling.

Kontrollprøver tatt til samme tider fra friske dykkere etter dykk til >25 m.

Blodet ble brukt i analyser for å modellere og sammenligne immuncelleaktivitet hos

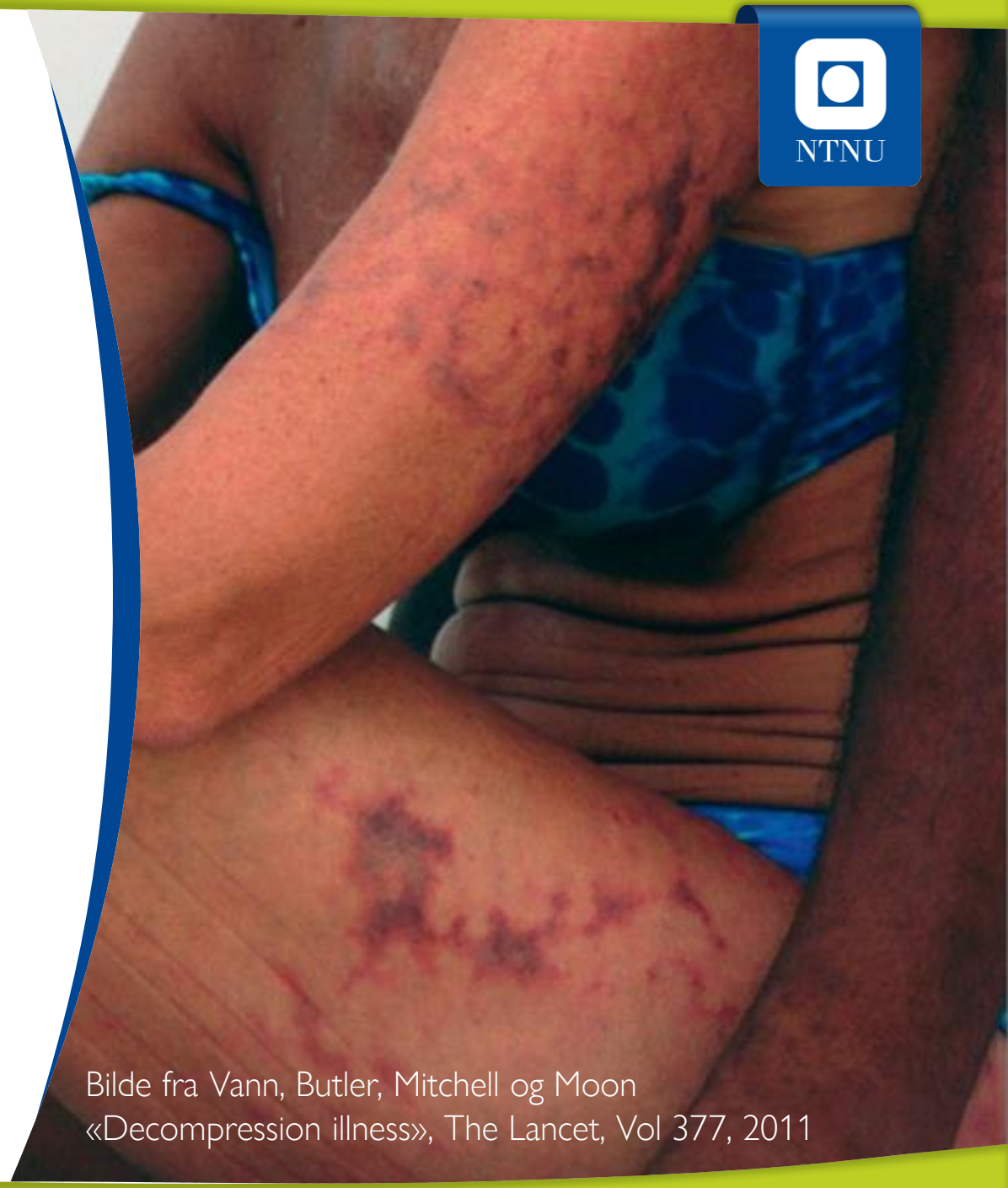
2) Syke dykkere før hyperbar oksygenbehandling og

3) etter oksygenbehandlingen

4) Friske dykkere

Kriterier for utvalg av syke dykkere

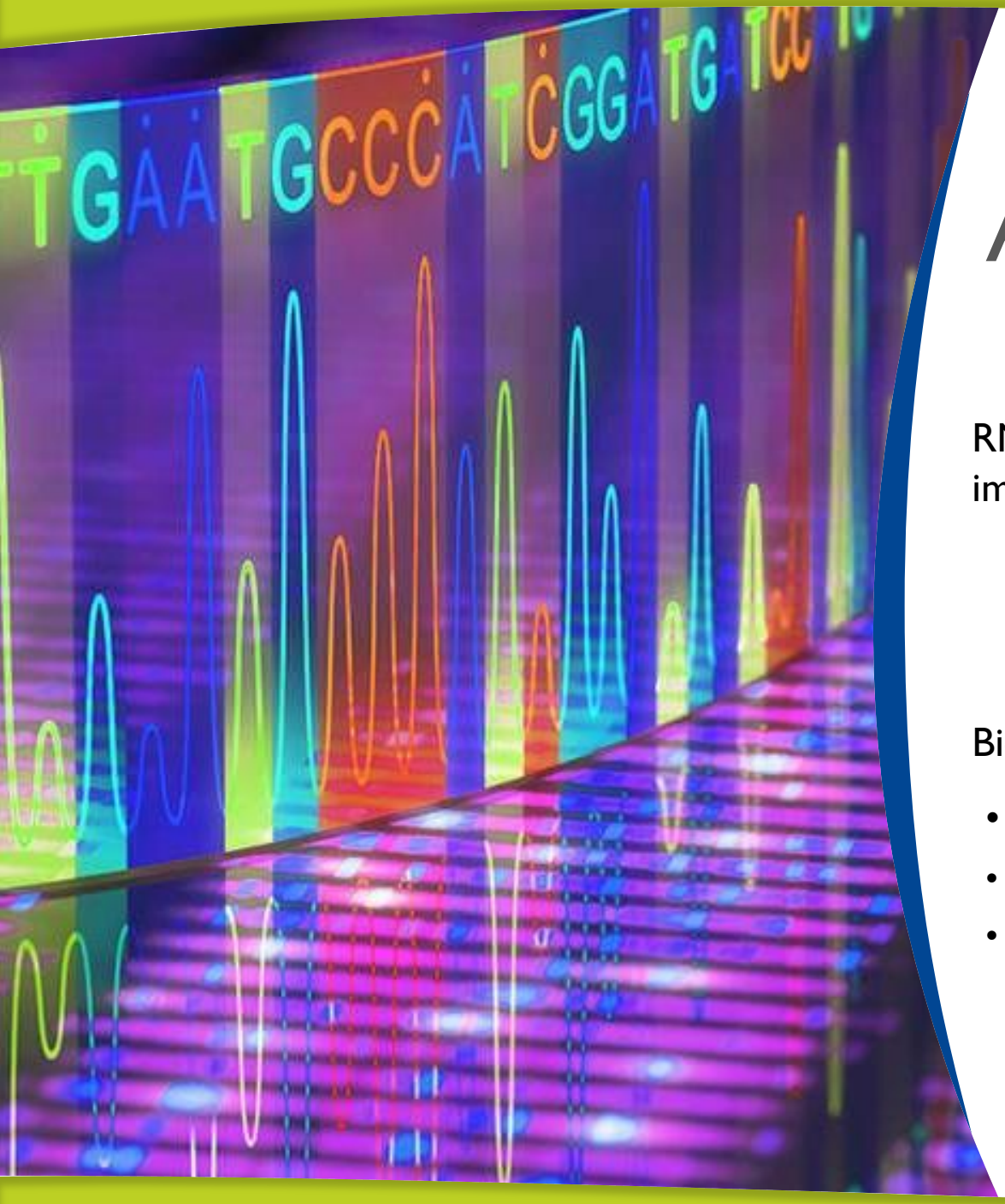
	Cases (n=7)
Inclusion Criteria*	Cutis marmorata rash within 8 hours of surfacing from a scuba dive, witnessed and confirmed by diving medicine physician.
	Presentation at the emergency department within 8 hours of surfacing from a dive.
	Fasted for 10hrs prior to T2.
	Age ≥ 18 years old.
Exclusion Criteria	Refusal of appropriate hyperbaric treatment.
	Performed strenuous exercise between the dive and T2.
	Ingested alcohol between the dive and T2.
*All inclusion criteria were required to be satisfied for recruitment.	



Bilde fra Vann, Butler, Mitchell og Moon
«Decompression illness», The Lancet, Vol 377, 2011

..og for friske kontrolldykkere

	Controls (n=6)
Inclusion Criteria*	Surfaced from a scuba dive with a ≥25 msw maximum depth without dive table violation.
	Surfaced from a dive within the preceding 8 hours.
	Subjected to diving physician questioning and physical examination at T1 and T2 to exclude DCS.
	Fasted for 10hrs prior to T2.
	Age ≥ 18 years old.
Exclusion Criteria	Underwent further diving before T2.
	Performed strenuous exercise between the dive and T2.
	Ingested alcohol between the dive and T2.
	Symptoms suggestive of DCS at T1, T2 or between T1 and T2.



Analysene

RNA-sekvensering for global kartlegging av genetisk aktivitet i immunceller fra dykkernes blod

det genererer enorme datamengder

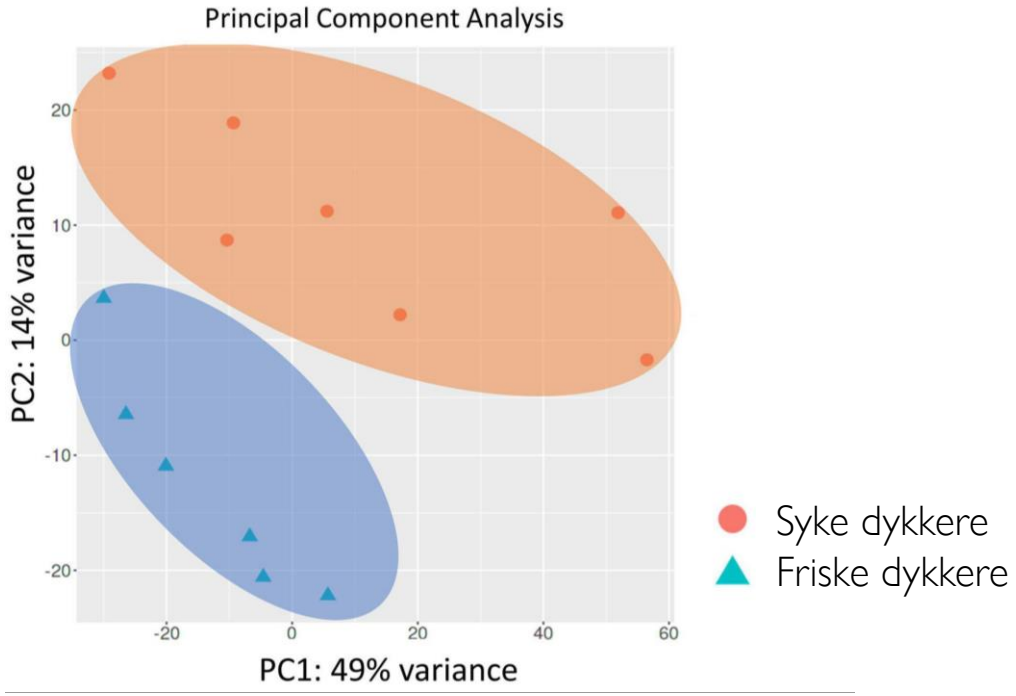
Bioinformatisk analyse av RNA-sekvensdata for å tolke immunresponser

- Hvilke immuncelletyper var mest påvirket ved trykkfallsyke?
- Hvor mye (mengde) og hvordan (funksjon) ble immuncellene påvirket?
- Hvordan endret responsen seg etter trykkammerbehandling?

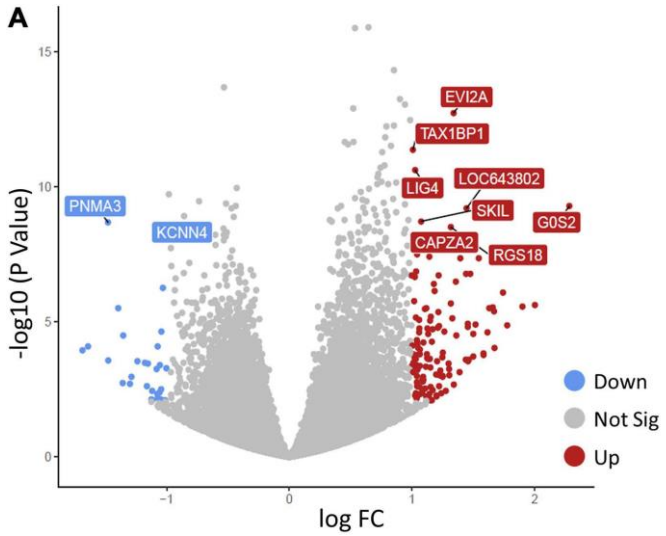
Hva fant vi? -Hovedpunkter

Syke og friske dykkere hadde *veldig* ulik immuncelleaktivitet i blod

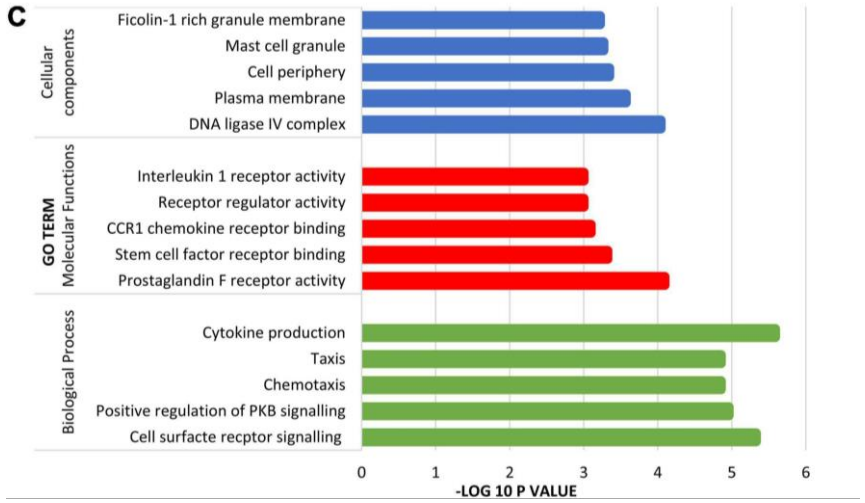
= Lovende utgangspunkt for den videre analysen ☺



Hos syke dykkere før trykkammerbehandling



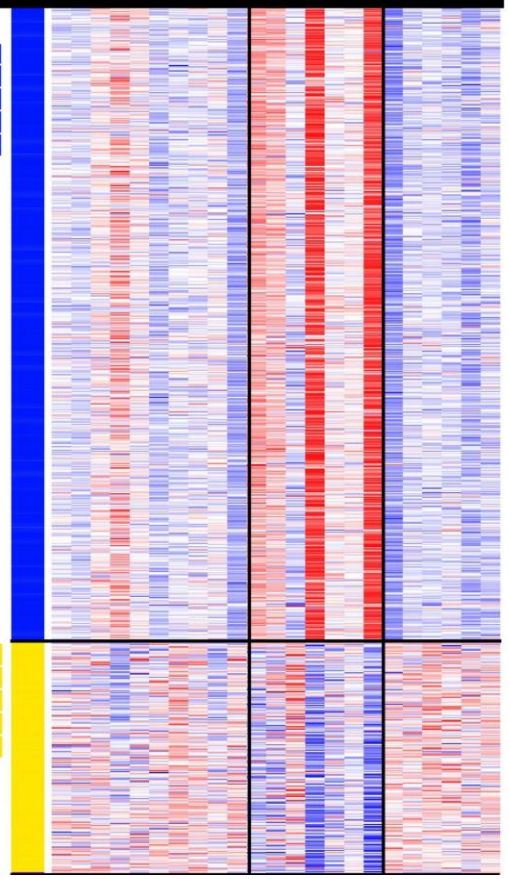
De viktigste *genene*



De viktigste *biologiske prosessene*

Hovedfunn ved trykkfallsyke

Cluster	Pathways	adj. P value
A	Myeloid leukocyte activation	2.80E-43
	Neutrophil activation	2.10E-31
	Leukocyte degranulation	1.60E-39
	Regulated exocytosis	2.80E-33
	Secretion by cell	4.60E-33
B	Immune system process	2.30E-22
	Cell surface receptor signalling pathway	5.90E-14
	Lymphocyte activation	1.30E-13
	Adaptive immune response	4.60E-11
	T-cell activation	2.00E-08



Høyere aktivitet ved trykkfallsyke

Lavere aktivitet ved trykkfallsyke

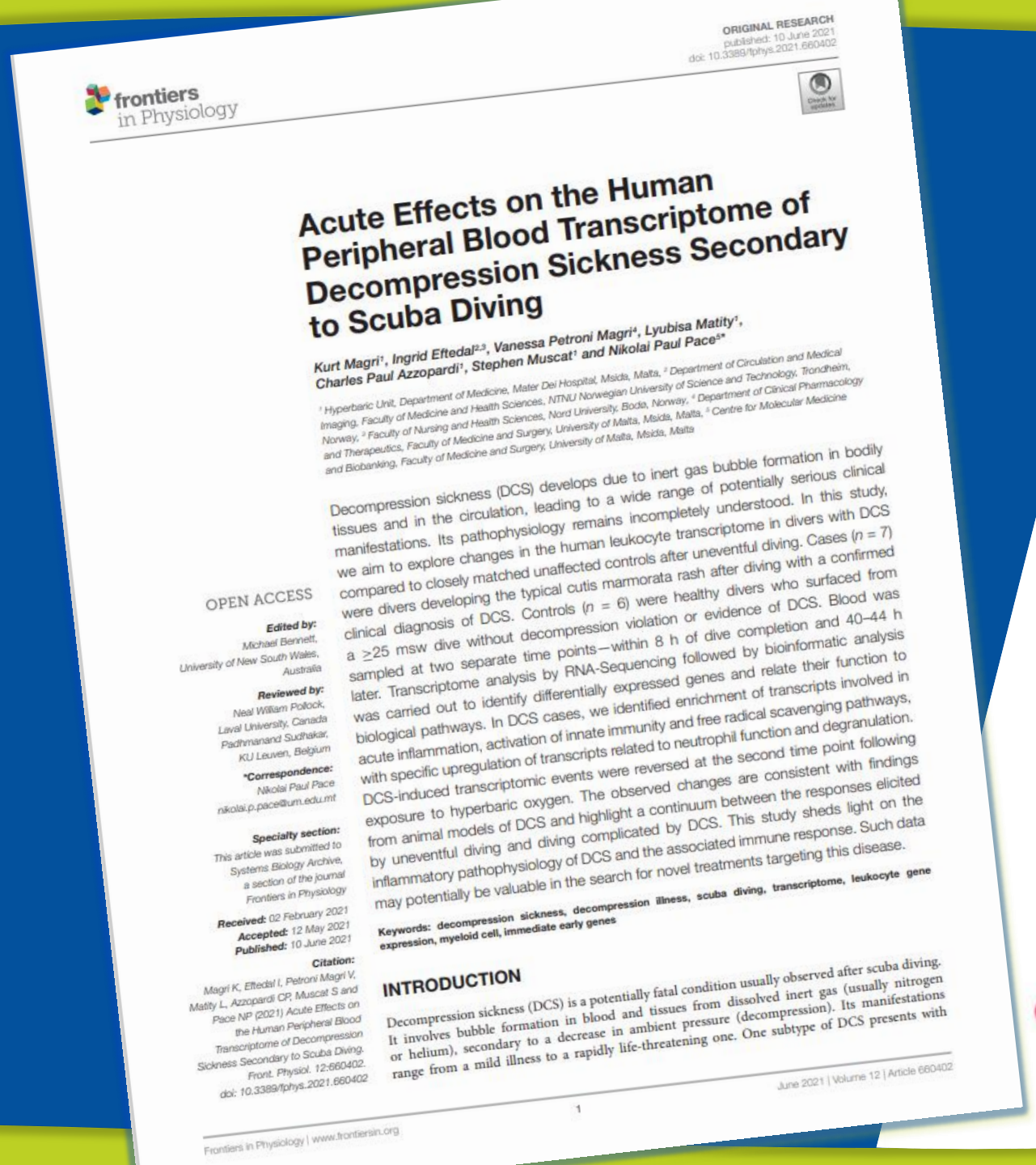
Hvordan kan resultatene brukes videre?

Hovedmålet er blodtester – biomarkører - som kan støtte diagnostikk og behandling for trykkfallsyke raskt og presist.

Resultatene er beregnet ut fra *ett* nivå av biologiske responser (RNA / genetisk aktivitet).

Vi trenger å vite om de også er målbare på *andre* nivåer som er hensiktsmessige for biomarkører: f.eks. overflatemarkører på immuncellene eller proteiner i blod.

Det vi har nå, er gode indikatorer for hvor biomarkørene kan finnes. Men veien til praktisk anvendelse er lang.



frontiers in Physiology

ORIGINAL RESEARCH
published: 10 June 2021
doi: 10.3389/fphys.2021.660402

Acute Effects on the Human Peripheral Blood Transcriptome of Decompression Sickness Secondary to Scuba Diving

*Kurt Magri[1], Ingrid Effedal[2,3], Vanessa Petroni Magri[4], Lyubisa Matity[1], Charles Paul Azzopardi[1], Stephen Muscat[1] and Nikolai Paul Pace[5]**

[1] Hyperbaric Unit, Department of Medicine, Mater Dei Hospital, Msida, Malta, [2] Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, NTNU Norwegian University of Science and Technology, Trondheim, Norway, [3] Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway, [4] Department of Clinical Pharmacology and Therapeutics, Faculty of Medicine and Surgery, University of Malta, Msida, Malta, [5] Centre for Molecular Medicine and Biobanking, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

Decompression sickness (DCS) develops due to inert gas bubble formation in bodily tissues and in the circulation, leading to a wide range of potentially serious clinical manifestations. Its pathophysiology remains incompletely understood. In this study, we aim to explore changes in the human leukocyte transcriptome in divers with DCS compared to closely matched unaffected controls after uneventful diving. Cases (n = 7) were divers developing the typical cutis marmorata rash after diving with a confirmed clinical diagnosis of DCS. Controls (n = 6) were healthy divers who surfaced from a ≥25 msw dive without decompression violation or evidence of DCS. Blood was sampled at two separate time points—within 8 h of dive completion and 40–44 h later. Transcriptome analysis by RNA-Sequencing followed by bioinformatic analysis was carried out to identify differentially expressed genes and relate their function to biological pathways. In DCS cases, we identified enrichment of transcripts involved in acute inflammation, activation of innate immunity and free radical scavenging pathways, with specific upregulation of transcripts related to neutrophil function and degranulation. DCS-induced transcriptomic events were reversed at the second time point following exposure to hyperbaric oxygen. The observed changes are consistent with findings from animal models of DCS and highlight a continuum between the responses elicited by uneventful diving and diving complicated by DCS. This study sheds light on the inflammatory pathophysiology of DCS and the associated immune response. Such data may potentially be valuable in the search for novel treatments targeting this disease.

Keywords: decompression sickness, decompression illness, scuba diving, transcriptome, leukocyte gene expression, myeloid cell, immediate early genes

OPEN ACCESS

Edited by:
Michael Bennett, University of New South Wales, Australia

Reviewed by:
Neal William Pollock, Laval University, Canada
Padhmanand Sudhakar, KU Leuven, Belgium

***Correspondence:**
Nikolai Paul Pace
nikolai.p.pace@um.edu.mt

Specialty section:
This article was submitted to Systems Biology Archive, a section of the journal Frontiers in Physiology

Received: 02 February 2021
Accepted: 12 May 2021
Published: 10 June 2021

Citation:
Magri K, Effedal I, Petroni Magri V, Matity L, Azzopardi CP, Muscat S and Pace NP (2021) Acute Effects on the Human Peripheral Blood Transcriptome of Decompression Sickness Secondary to Scuba Diving. Front. Physiol. 12:660402. doi: 10.3389/fphys.2021.660402

INTRODUCTION

Decompression sickness (DCS) is a potentially fatal condition usually observed after scuba diving. It involves bubble formation in blood and tissues from dissolved inert gas (usually nitrogen or helium), secondary to a decrease in ambient pressure (decompression). Its manifestations range from a mild illness to a rapidly life-threatening one. One subtype of DCS presents with

NTNU

European Union
European Social Fund

L-Università ta' Malta

Forskningsrådet
The Research Council of Norway

equinor