ONCOBIOME
Microbiota against cancer
International research program

REVIEW #3
September 2020

First and bigger network and biobanking of cancer patients stools for building up gut oncomicrobiome signatures for a better diagnosis and treatment of malignancies in europe.

SPECIAL EDITION
COVID Health Crisis

The ONCOBIOME network gathered a couple of collaborators to embrace the health crisis and to face the challenge on how to contribute to increase significant knowledge on SARS-CoV-2 biology and clinical management in cancer free and cancer patients.

Pr. Laurence Zitvogel
Gustave Roussy - Villejuif, France

ONCOBIOME update

Needless to say that the feces collection and patients' accrual have been stopped with an expected delay in the specific deliverables of ONCOBIOME. However, the good piece of news is that Genizyme extraction milieu to condition the microbial DNA harvested from stools prior to MG analyses kills/neutralizes CoVs-2 viral particles, allowing to expedite transportation of specimen across countries and sequencing analyses.

July 2020, most of ONCOBIOME Principal Investigators could continue or restart patients' inclusions and sequencing analyses.

Research must go on...

The coordinator (Pr. Zitvogel, Dr. Derosa, Dr. Marabelle), Gustave Roussy - France, opened a clinical trial at Gustave Roussy, called **ONCOVID "Epidemiological prospective study on the incidence and severity (mortality) of the current pandemic COVID19 and therapeutical benefit of the combination of hydroxychloroquine + azithromycine in severe cases in a population of cancer patients treated at Gustave Roussy Cancer Center"** EuDRACT N° 2020-001250-21.

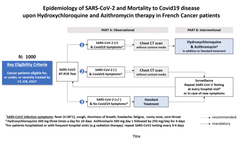
In parallel, a large ancillary study has been launched based on a prospective collection of up to 8,000 serial and paired (longitudinal) biological samples from 480 patients (blood, serum, oropharyngeal swabs, urine, tongue swabs, and non systemic bronchoalveolar lavages in rare cases), encompassing 53 COVID19 positive and the rest being COVID19 negative cancer patients.

Research objectives

1. High dimensional immunological phenotyping based on mass and spectral multiparametric flow cytometry on blood cells,
2. Functional assays to assess innate (cross-talk between plasmacytoid dendritic cells and NKcgdT cells from blood) and CD4+ and CD8+ T cell -based cognate immune responses against SARS-CoV-2 and seasonal human coronaviruses (for cross-reactivity analysis),
3. Microbiome studies (on pharyngeal, tongue swabs, blood and urine specimen),
4. Effects of HCQ+AZY on patients outcome, immunological and virologic parameters,
5. Metabolomics changes during Tocilizumab therapy in responders versus non responders (Dr Marabelle, Dr Danlos, Dr Kroemer).

Many of the investigations are ongoing and results will be coming soon during this fall.

ONCOVID design



Zoom on ONCOBIOME's publications

Cells - Silvin *et al.*

This publication shows that severe COVID19 is associated with signs of emergency hematopoiesis, characterized by bone marrow (and/or pulmonary) exodus of pre-neutrophils and immature neutrophils coinciding with a peak in alarmin release (centered around serum S100A8/A9 calprotectine).

High dimensional flow cytometry, combined with single cell sorting and transcriptomics deconvolution to allow design of trajectories of cell functional status, revealed that these immature neutrophils are accompanied by the loss of non conventional monocytes and harbor a transcriptomic fingerprint defined by inflammatory and immunosuppressive (NF-kB, IL-1b, ROS, NOS) markers.

One of the best hallmark of the switch between a mild to moderate /severe disease status is the concentration of calprotectine, a prognosis parameter outperforming IL-6 concentration. Indeed, calprotectine raised abruptly and correlated with immature neutrophils, D dimers and fibrinogen, presumably underlying immunothrombosis. This signature of S100A8/A9 expressing immature neutrophils and monocytes was recovered in bronchoalveolar lavages, suggesting that they may initiate and/or maintain respiratory distress in these patients.
The coordinator reported the clinical outcome of >150 patients diagnosed with COVID19 (Albiges L, Nature Cancer in press) aligning the most significant clinical parameters associated with severity in cancer patients. Solid and hematological malignancies were studied.

Nature Cancer - Derosa *et al.*

During this time, other studies reported that while COVID19 incidence was not superior in cancer patients, the lung infection tended to be more severe, and chemotherapies as well as immunotherapies preceding the infection or at the onset of early symptoms accelerated disease severity. *Dr. Lisa DEROSA from ONCOBIOME - Gustave Roussy, France - wrote a review article in Nature Cancer summarizing the prototypical features of COVID19 in cancer patients, and discussed the role of co-morbidities and co-medications in disease outcome.*

Other projects of interest

Collaboration with the French Biotech. Valomer

Given that SARS-CoV-2 is replicating in the upper digestive tract, and that ileal epithelial cells harbor ACE2 receptor (SARS-CoV2 receptor), **the question as to how viral replication could compromise the epithelial barrier fitness and facilitate bacterial translocation in the blood was adressed. In fact, it is reported that bacterial and viral signals could synergize or antagonize each other, depending on the timing and sequencing of both signals in myeloid cells.**
Pr. Zitvogel launched a collaboration with the French Biotech. Valomer to analyze up to 150 blood specimen (53 COVID+ and controls) in metagenomics to delineate bacterial signatures associated with immune and inflammatory parameters and disease outcome.

MG analyses of the tongue swabs to ONCOVID

Dr. Nicola Segata, University of Trento, accepted to run the MetaGenomics analyses of the tongue swabs to ONCOVID to characterize a potential deviation in the oral microbiome.
This exciting work is ongoing and might unveil a missing link in our understanding on the pathophysiology of this peculiar coronavirus infection.

Collaboration with Dr. Didier Raoult at the IHU Mediterranée Infections (France)

In parallel, we collaborated with Dr. Didier Raoult at the IHU Mediterranée Infections to study memory T cell responses against SARS-CoV-2 in cancer and cancer free patients during disease onset and at recovery, as well as seasonal 229E and OC43 coronaviruses, to nail down a putative cross-reactivity of memory T cells. These T cell assays will be aligned with other principal investigators from AP-HP (Pr. Gorochov, Pr. Tartour) and Champalimaud Foundation (Pr. Markus Maeurer) as well as Spallanzani Infectious Disease Center (Dr. Piacentini, Dr. Ippolito) to standardize methodologies and pinpoint T cell epitopes of clinical significance.
We are currently gathering all the data of this ongoing work and anticipate to be able to release more pieces of information within the fall, that could guide the clinical management of the upcoming winter outbreak in the cancer patient population.

References

Silvin A. *et al.* Cell. 2020 Aug 5;S0092-8674(20)30993-4
Derosa *et al.* Nature Cancer (in revision)
Derosa *et al.* Nature Rev.Urol. In press
Albiges *et al.* Nature Cancer in press

VISIT THE ONCOBIOME WEBSITE

Visit **www.oncobiome.eu** to be updated on the latest ONCOBIOME news.

KEY DATES

Meet - virtually - the ONCOBIOME team at the following events and learn more about the consortium:

- ESMO VIRTUAL CONGRESS / Sept 19th – 21th
- SITC / Nov 11th

KEY FIGURES

17
teams across 9 european countries and Montréal

9000
cancer patients

25 000
stool biobanking

€
15
million euros

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Se désinscrire

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Titre