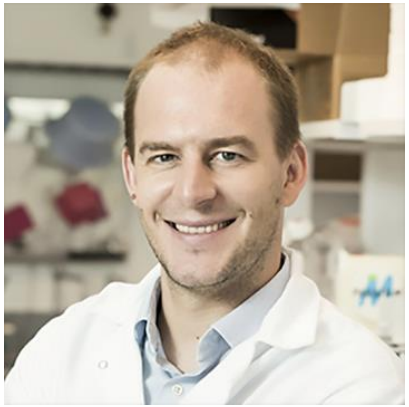
CTL CENTER FOR TECHNOLOGY LICENSING AT CORNELL UNIVERSITY

Iwijn De Vlaminck Lab

Cell-free DNA Diagnostics

Iwijn De Vlaminck Lab



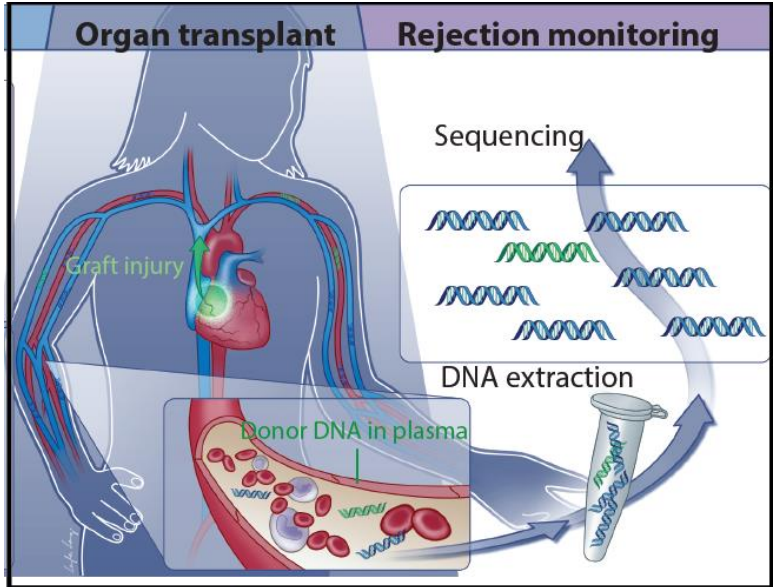
CornellEngineering

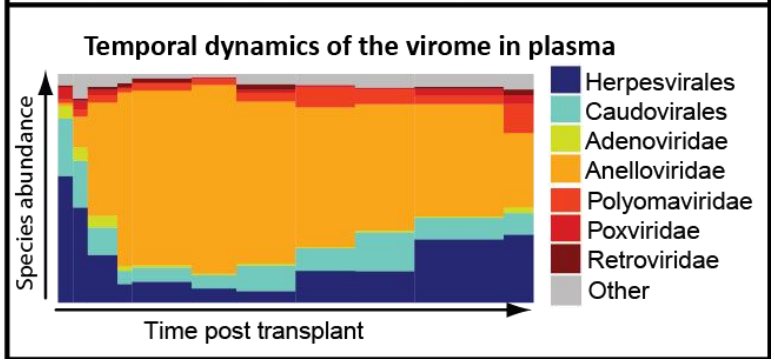
- Assistant Professor of Biomedical Engineering, Cornell University
- Postdoc, Stanford University

  Non-invasive DNA sequencing based diagnostics of transplant rejection and infections

Iwijn De Vlaminck Lab @Cornell is applying approaches from biophysics and genomics to biomedicine

- Liquid biopsies for infectious and immune-mediated diseases
- Precision monitoring of infection, host tissue injury, organ transplant rejection, graft-versus-host disease





Circulating Cell-free DNA

- cfDNA potential in **diagnostic medicine**:
  - **abundance**: 10-100 billion molecules of cell-free DNA in 1 mL of plasma
  - **origin**: cell-free DNA fragments are remnants of cell death across the body
  - **access**: cfDNA circulate in blood and vascularized tissue and can be accessed noninvasively
  - **short lifetime**: cfDNA is cleared from blood within 60 minutes: a very dynamic window into health

De Vlaminck Lab Publications

The proportion of donor specific cell-free DNA in blood as a marker of transplant rejection: not an absolute. De Vlaminck I. Clinical Chemistry, in press (2020).

A liquid biopsy for COVID-19. Cheng AP et al. Submitted, preprint (2020)

Blood-borne biomarkers may help predict COVID-19 mortality. De Vlaminck I Science Translational Medicine (2020).

Donor-derived Cell-free DNA is Elevated During Allograft Rejection after Lung Transplantation. Khush K et al. ERJ Open Research, in press (2020).

Transcriptomics of Acute Rejection in Kidney Allografts. Verma A et al. JCI Insight (2020).

Separating the signal from the noise in metagenomic cell-free DNA sequencing. Burnham P et al. Microbiome, 8,18 (2020).

Adding insult on injury: immunogenic role for donor-derived cell-free DNA? Dholakia S, De Vlaminck I, Khush K Transplantation (2020).

A cell-free DNA metagenomic sequencing assay that integrates the damage response to infection. Cheng AP et al. Proceedings of the National Academy of Sciences (2019).

Gut Uropathogen Abundance is a Risk Factor for Development of Bacteriuria and Urinary Tract Infection. Magruder M et al. Nature Communications (2019).

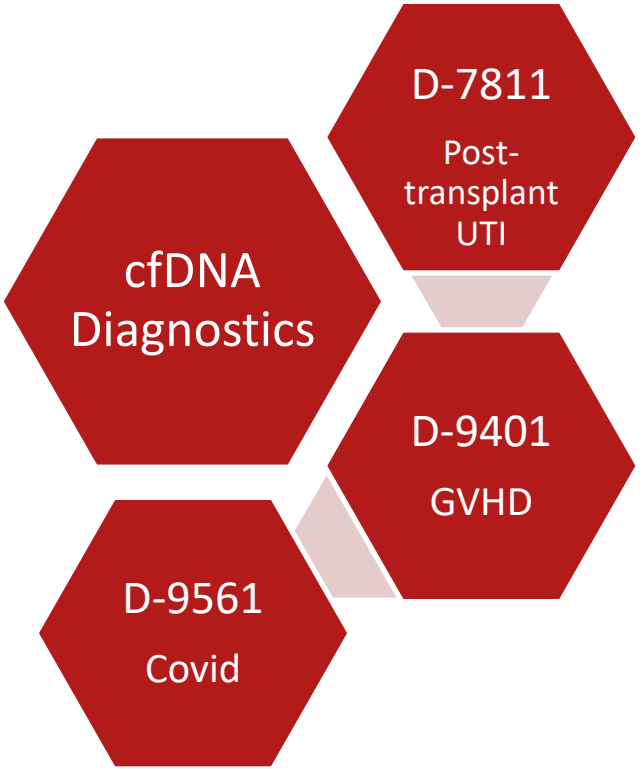
Simultaneous multiplexed amplicon sequencing and transcriptome profiling in single cells. Saikia M, Burnham P, et al. Nature Methods (2019).

Urinary cell-free DNA is a versatile analyte for monitoring infections of the urinary tract. Burnham, P, Lee, JR, De Vlaminck I, et al. Nature Communications (2018).

cfDNA diagnostic platform

Simultaneous quantification of viral and bacterial pathogens and the degree of tissue-specific host injury

- D-7811 – UTI monitoring for transplant patients
  - Methods to detect cfDNA of bacteria and viruses in urine and monitor urinary tract infections using single-stranded DNA library preparation for next-generation sequencing
- D-9401 – Graft-vs-host disease + infection
  - cfDNA test to detect graft-versus-host disease and microbial infections after hematopoietic cell and other transplants
- D-9561 – Covid-19 severity and organ damage
  - cfDNA in blood reveals cell, tissue and organ specific injury associated with COVID-19 and informs clinical management

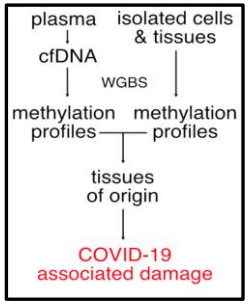


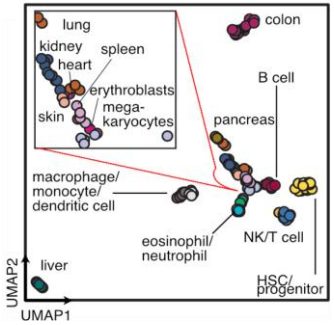
D-9561: Minimally invasive organ-specific COVID-19 diagnostics

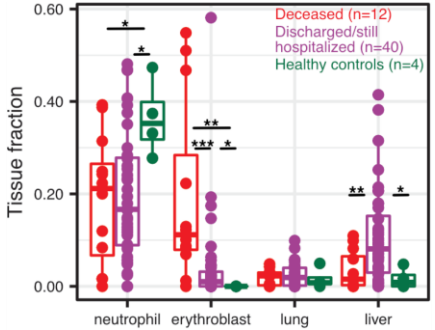
Technology Overview

COVID-19 patients present with disparate clinical manifestations leading to different life-threatening complications and requiring different treatments. There is an urgent need to quickly assess disease severity and to quantify injury to multiple organs simultaneously in order to monitor patients and guide clinical management.

This invention describes a minimally invasive molecular test to assess tissue and organ-specific injury due to COVID-19 by quantifying overall and tissue-specific circulating cell-free DNA (cfDNA). cfDNA are short fragments of DNA circulating in blood, plasma, and urine that originate from debris of dead cells from across the body and carry tissue-specific methylation markers. This diagnostic method was applied in two independent patient cohorts and detected evidence of significant injury to liver and lung and involvement of red blood cell progenitors associated with severe COVID-19. Test results were predictive of the WHO disease progression stage, the need for aggressive clinical measures including ICU admission and mechanical ventilation, and in-hospital mortality.







Potential Applications

- Rapid and granular assessment of COVID-19 disease severity
- Early detection of tissue or organ-specific injury to inform treatment decisions
- On-going monitoring of disease progression and response to treatment
- Surrogate biomarker for clinical trials of candidate COVID-19 treatments

Advantages

- Minimally invasive and rapid
- Tissue and organ specific injury diagnosis

Read more on Flintbox

Inventors:

Iwijn De Vlaminck, Alexandre Pellan Cheng

Patents: Filed

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Publication:

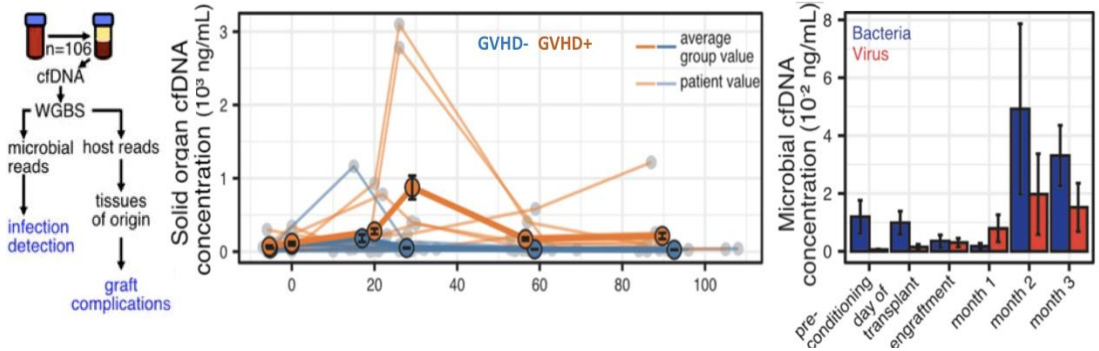
Cheng AP et al. Cell-Free DNA in Blood Reveals Significant Cell, Tissue and Organ Specific injury and Predicts COVID-19 Severity. medRxiv 2020 Jul 29

D-9401: Minimally invasive test for graft-versus-host disease and infections after transplants

Technology Overview

Over 30,000 patients undergo hematopoietic cell transplants (HCT) each year for treatment of blood disorders. Up to 50% of patients develop graft-versus-host disease (GVHD). To manage the risk of GVHD, patients receive immunosuppression therapy, putting them at risk of infections. Early GVHD diagnosis, monitoring response to GVHD treatment, and assessing infections are critical for preventing serious complications including organ failure and death. Current clinical methods require confirmation by invasive procedures such as a biopsy of the gut, skin, or liver, while protein marker tests are limited to few tissue types and do not detect infections.

Inventors disclose a minimally invasive blood test to simultaneously detect tissue-specific injury and microbial pathogens after HCT. The test utilizes genome-wide profiling of tissue-specific methylation marks within circulating cell-free DNA (cfDNA). In a prospective clinical study, the test predicted GVHD within one month of transplant and identified viral and bacterial infections.



Potential Applications

- Early diagnosis and treatment monitoring of GVHD after HCT
- Detection of viral and bacterial infections post HCT

Advantages

- Minimally invasive, rapid tissue-specific injury detection
- Simultaneously informs both GVHD and infection diagnosis
- Compatible with existing next-generation sequencing workflows

Read more on Flintbox

Inventors:
Alexandre Pellan Cheng, Iwijn De Vlaminck

Patents: Filed

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Publication:

Cheng AP et al. Cell-free DNA Tissues-of-Origin Profiling to Predict Graft versus Host Disease and Detect Infection after Hematopoietic Cell Transplantation. bioRxiv. 2020 Apr 29.

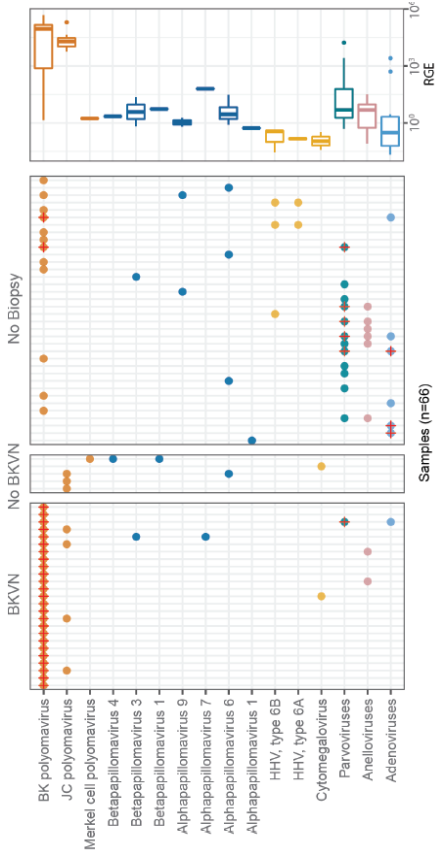
D-7811: Methods of detecting cell-free DNA in biological samples

Technology Overview

Urinary tract infections (UTI) occur at a high rate among kidney transplant recipients. The incidence of bacterial UTI is at least 20% in the first 3 months and 50% 36 months after kidney transplantation. Conventional culture methods do not detect viruses or organisms that are not cultivable in vitro.

Cornell inventors developed a method that leverages the presence of a large amount cell-free DNA (cfDNA) to detect and monitor viral and bacterial infections using Next Generation Sequencing (NGS). cfDNA are nucleic acid fragments released in the bloodstream during apoptosis or necrosis. They offer a non-invasive, rapid, sensitive, and accurate method of diagnosis and monitoring for cancer, infectious diseases, pregnancy, and solid-organ transplant rejection. Proposed DNA library preparation method enables robust sequence analyses of urinary cfDNA from just one ml of urine.

As a proof of concept, the team assayed urine samples collected from renal transplant recipients with clinically confirmed UTIs. Using the novel method, they were able to confirm infections, identify co-infecting microbes, determine the replication rate and growth dynamics of various bacterial strains without the need for an annotated genome, making possible prediction of the efficacy of antibacterial drug therapies.



Potential Applications

- Detection and monitoring of infections
- Research tool to predict the efficacy of antibiotics

Advantages

- Enable detection of organisms that are not cultivable in vitro
- Enable detection of viruses
- Non-invasive sample extraction (Urine collection)

Read more on Flintbox

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Publication:

Vlaminck I. et al. A cell-free DNA metagenomic sequencing assay that integrates the damage response to infection. bioRxiv 5/24/19