Project leader:
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Other team members:
Tom Blydt-Hansen, BC Children Hospital

Title of the project:
Personalized risk assessment in pediatric kidney transplantation using metabolomics data

Scientific Summary of the Project (one paragraph):

Kidney transplantation is the most effective treatment for end-stage kidney failure and improves both survival and quality of life. It is not, however, a cure and most young people will experience complications that precipitate allograft failure. At present, children are all treated with a standard protocol for immune suppression, which ignores the wide heterogeneity in both immune responses and susceptibility to complications. As a result, some children suffer complications for excessive immune suppression whereas others may suffer rejection from insufficient immunosuppression. We aim to study how the metabolism state of the kidney recipient affects the evolution of the immune response to the allograft after transplant. Our goal is to identify a metabolomic signature using ***pre-transplant serum samples*** to support a precision-medicine approach to immunosuppressive treatment that can be tailored to the alloimmune risk-characteristics of each patient. Providing a personalized risk assessment would permit tailoring of treatment to optimize management of immunosuppression and avoid complications related to unnecessary treatment.

Key objectives of a Multi-year Team Grant:

- Develop a unique pre-transplant serum immunometabolomic signature that predicts risk for alloimmune transplant failure.
- Validate the identified signature in a multi-center cohort
- Evaluate the changes in immunometabolomic profiles post-transplant that are associated with immunosuppressant treatment, and with changes in clinical status (nutrition, uremia, infection) that are expected to influence the immunometabolomic phenotype of transplant recipients.

The most relevant outcome after transplant related to the allograft is kidney failure, but this is associated with several more proximal outcomes that may be modifiable. These include the development of donor-specific antibodies, the incidence of acute rejection and the occurrence of donor-derived viral infections. These complications are known to be influenced by numerous factors that may be identifiable at the time of kidney transplant, such as donor factors (e.g. donor age, hypertension, cause of death, prior viral illness), immune factors (level of HLA mismatch between the donor/recipient), recipient factors (severity of renal failure, time on dialysis, malnutrition, prior viral illness) and treatment factors (induction therapy, initial immunosuppression levels). This information becomes available at different stages in the transplant process: pre-transplant recipient factors; peri-operative

donor/immune factors; and early post-operative treatment-related factors. At each stage, risk profiling could be adjusted with addition of new information.

To understand how the metabolism state of the kidney recipient affects the evolution of the immune response to the allograft after transplant, we will look for patterns of serum metabolites that are associated with alloimmune kidney transplant failure. We aim to identify a metabolomic signature using ***pre-transplant serum samples*** to build risk prediction models to individualize management and treatment of individual patients and thus optimize graft outcome and quality of life.

Dr. Blydt-Hansen team has collected metabolomics data from 180 adult and pediatric kidney transplant recipients at the time of transplantation, and has access to additional post-transplant samples for further testing to establish persistence of metabolomic phenotypes. Additional detailed information on patient characteristics, treatment, complications and outcomes after kidney transplantation are also available to integrate with the metabolomics data. Furthermore, surrogate markers of acute inflammation (urinary chemokines and metabolomics) and surrogate indicators of transplant tolerance (flow cytometry for regulatory T cells) will be available in a subset of the cohort.

We will have access to many more samples, which we can analyze with additional funding. As a long-term objective, we aim to apply for further grant funding of a multicenter trial to extend the validation of the immunometabolomic signatures at transplant and for serial monitoring post-transplant. In this joint project we aim to demonstrate the benefits understanding metabolomics data and using it to build strong and powerful models to assess risk of allograft kidney failure and related complications. A post-doc will help us advance in this project and complete 3 preliminary aims outlined below. Based on the results of this initial study, we will apply for additional funding to achieve our long-term objectives.

Data Science Research Problems to be Addressed in the Multi-year Grant:

Dr. Cohen Freue research lab has extensive expertise in the analysis of –omics data in transplantation as well as other conditions. In particular, her group has recently developed robust regularized regression methods that can be used to identify the most relevant metabolites associated with graft outcome. However those methods cannot be used to build classifiers where the response variable is binary (or categorical). Most available methodologies to build classifiers are extremely sensitive to outliers, which are very common in metabolomics data, due for example, to technical problems in sample preparation or patients with rare molecular profiles. Thus, robust classification methods that can identify a relatively small subset of features among a large number of available are needed to effectively interrogate the rich information contained in the data. In addition, metabolomics data is characterized by a large proportion of samples measured under the limit of detection. Unless properly addressed methodologically, these characteristics may yield incorrect results and conclusions. The methods developed by the group will not only serve for the aims of the current project but also help to cover an existing gap in data science methodologies. Dr. Cohen Freue will also supervise the implementation of state-of-the art machine learning techniques to analyze the collected data, as well as the development of new methodologies tailored to address specific problems observed.

Key Milestones to be Carried Out in the First Year:

Aim 1: use machine learning methods (existing and newly developed by the group) to build a metabolomics classifier to predict long-term outcome (allograft survival).

Because of the availability of surrogates that associate well with long-term oucome, we also aim to train classifiers on risk for acute rejection, inflammatory signalling (urinary chemokines), graft injury and inflammation (urinary metobolomics), function (eGFR decline over year 1 post-transplant), clinical over-immunosuppression (incidence of donor-derived viral infections) and indicators of tolerance (proliferation of regulatory T cells measured by flow cytometry). We anticipate substantial overlap in metabolite patterns associated with long-term alloimmune outcomes, and those associated with the surrogate outcomes indicated above.

Aim 2: integrate the metabolomic risk profiles with other signatures developed separately from immune and treatment characteristics of recipient and donor data.

This approach will enable the characterization of a more comprehensive risk-profile for transplant recipients. The primary outcome of interest will be kidney allograft survival, as well as near-term surrogate risk factors as described in the first Aim.

Aim 3: study the relation of the identified pre-transplant metabolomics signature with post-transplant urinary biomarkers that have been extensively evaluated by Dr. Blydt-Hansen research group.

These include CXCL10, a chemokine that is expressed in an interferon-gamma-dependant manner in the setting of acute rejection; and urine metabolite signatures that we have validated in association with acute rejection and other immune/non-immune types of kidney allograft injury. These biomarkers have particularly high utility, in that they are easily measured and there is ample access to samples obtained by sequential monitoring. Because of accessibility to repeated sampling, the trajectory of these indicators can be evaluated to identify latent classes within the cohort in an unsupervised manner. The identified classes are useful for the training of classifiers that identify pre-transplant metabolomic and comprehensive patterns of risk. Such risk-prediction algorithms would have important utility in predicting risk in transplant candidates, and adapting the approach to treatment in a precision-medicine approach to transplant care.