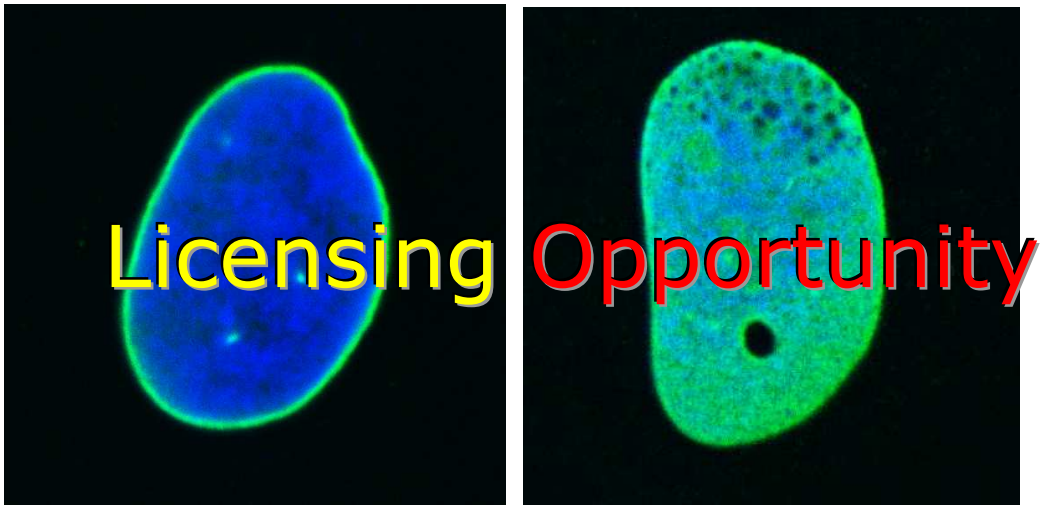


Prediction of Nuclear Envelope-related diseases

- **Type of technology: diagnostics & screening platform**
- **Indication: the diagnosis of dilated cardiomyopathy, muscular dystrophy and partial lipodystrophy**
- **Phase: Preclinical**
- Early detection of nuclear envelopathies and the prediction of the severity of this disease.
- Allows for distinguishing between different types of laminopathies.

The challenge:

It has recently been discovered that mutations in nuclear lamin proteins give rise to a wide range of inherited diseases, collectively termed laminopathies.

Laminopathies include muscular dystrophies, partial lipodystrophy syndromes, peripheral neuropathies, progeroid syndromes and conditions that lead to severe developmental abnormalities or death *in utero*. Laminopathies are often caused by a single point mutation in the lamina A/C gene. However, this single mutation can have an extremely variable impact on the pathophysiological development of the disease. Within family members who carry identical mutations, some people develop a severe laminopathy phenotype, resulting in early death due to heart failure, whereas siblings can remain disease-free. Thus, routine screening for genetic defects in the lamina A/C gene does not reliably predict instigation and/or development of the disease.

Laminopathies are characterized by several morphological abnormalities of the nuclear envelope. While these abnormalities can be readily visualized, no clear correlation with severity of the disease has been established as yet.

It has also been described to assess nuclear membrane abnormalities by performing mechanical loading on cells. Laminopathy cells showed a significant loss of mechanical strength in experimental setups. However, these experiments are difficult to perform and are not suitable in routine screening setups.

Our solution:

Our scientists identified a number of markers for correct cellular compartmentalization that are indicative of nuclear membrane integrity predicting disease severity. This assay can be performed in a routine laboratory setting, and can provide a novel method for determining the state of nucleo-cytoplasmic compartmentalization wherein the presence of nuclear markers outside of the nucleus is determined.
Applications of this method are the diagnosis of nuclear envelopathies, for predicting the severity of a nuclear envelopathy, or for selecting a drug against a nuclear envelopathy.

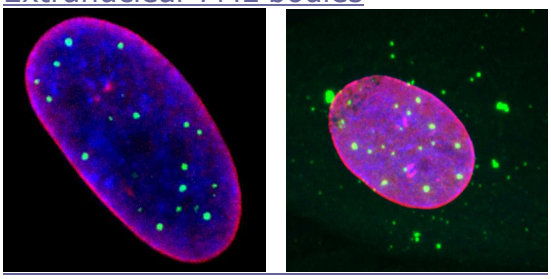
Scientific background:

Clearly, the association of NE proteins with such a wide range of diseases implies important functions for these proteins in the normal development and/or maintenance of many different tissue types. Indeed many NE proteins have differential expression profiles during development and have been implicated in a range of cellular functions including the maintenance of cellular architecture, apoptosis, DNA replication and transcription.

Importantly, lamins, which appear as a prominent rim-like labeling of the nuclear envelope using immunofluorescence, interact with and apparently stabilize several other structural NE proteins, such as emerin and nesprins. In addition, the appropriate distribution of nuclear pore complexes in the nuclear membrane is maintained by lamins.
In normal cells, a strict physical separation between nuclear and cytoplasm macromolecules is maintained by the nuclear envelope and the nuclear pore complex. Macromolecules with a physical size over 60kDa can normally only enter or leave the nucleus in interphase cells by active transport via the nuclear pore complex. Compartmentalization is critical for the functioning of cells: it ensures a correct and controlled localization of several transcription factors and signaling proteins.

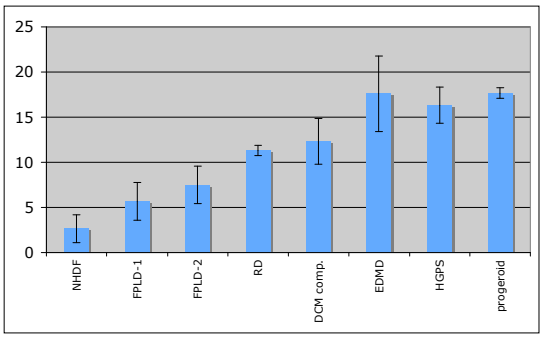
Preclinical data:

Extranuclear PML bodies



In normal cells (left) PML-NBs (green) are only found within the nucleus (blue with red rim). In diseased cells (right) PML bodies can also be found in the surrounding cytoplasm, indicating nuclear membrane failure and predicting laminopathy devlopment.

Table 1: Percentage of cells with extranuclear PML bodies in different laminopathies



Note the increased percentage of extranuclear PML-NBs in severe laminopathies, while extranuclear PMLS-NBs are detected in less then 3% of the control NHDF cells.

Collaboration between CARIM and GROW

CARIM

The Cardiovascular Research Institute Maastricht (CARIM) of the University of Maastricht has expertise in a wide range of areas, ranging from molecular biology to population-based studies. Its goal is to focus on clinically important questions, integrating knowledge from molecule to patient. CARIM is internationally renowned for it's research in the cardiovascular disciplines. In various reviews performed by the Royal Netherlands Academy of Arts and Sciences CARIM received the highest grading possible for its research and training program. Since 2007 BioMedbooster has started two new Ventures and closed nine license deals exclusively from CARIM-originated IP.

GROW

GROW is the School for Oncology & Developmental Biology and aims to carry out high quality scientific research in the field of early human development (normal and abnormal growth and differentiation) and in the field of oncology (abnormal growth and differentiation). The output of GROW shows an increasing number of peer reviewed papers, amongst others in the renowned Nature Reviews Cancer. Recent valorisation of GROW-originated IP: Joint development of anti-VEGF vaccine with Pepscan BV.

Inventors:

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- University of Ghent, Dept. of Molecular Biotechnology, Bio-imaging and Cytometry Unit: prof. dr. P. v. Oostveldt, PhD, Dr. W. de Vos, PhD.

IP status:

- Patent application filed

Licensing opportunity:

- Available for licensing
- Additional information is available upon execution of a Confidentiality Agreement

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