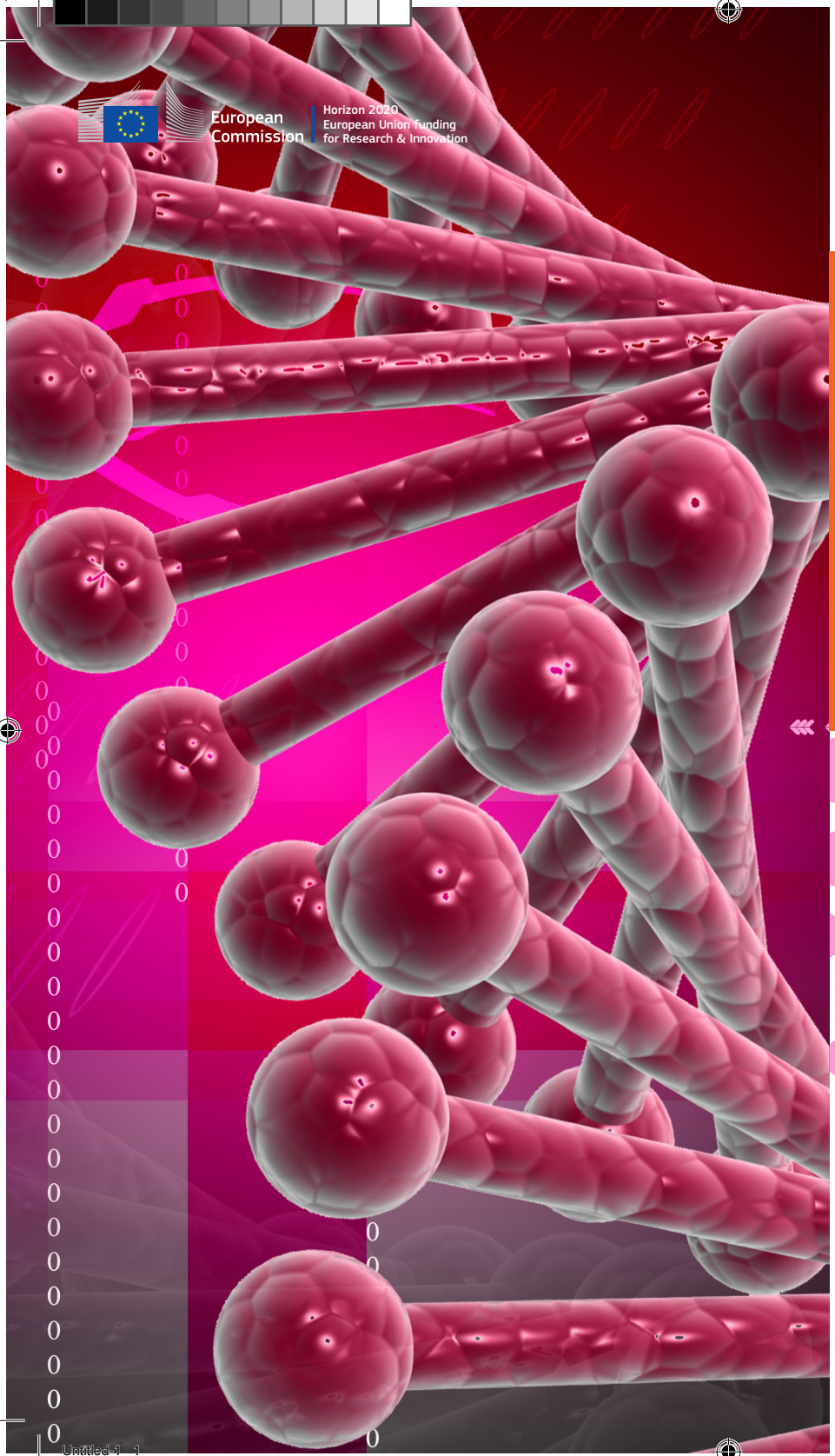


# Cancer research

2014

European Research Council

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# Introduction

Cancer is among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012 according to the World Health Organization. According to the same source, it is expected that annual cancer cases will rise from 14 million in 2012 to 22 million by 2030. Research on cancer development, treatment and prevention, as well as basic research in this area, is essential to reduce the burden of this disease.

Research specialisms in the field of cancer funded by the European Research Council (ERC) include diverse topics ranging from cancer metabolism, microenvironment, metastasis, epigenetics, angiogenesis, drug resistance, immunity to treatment and epidemiology, amongst others. More than 100 proposals on cancer research have been funded so far, and even more projects in the Life Sciences have a strong cancer component. To date, the ERC has invested over €200 million in cancer research.

The ERC is the first pan-European funding body designed to support investigator-driven frontier research and stimulate scientific excellence across Europe. It aims to support the best and most creative scientists to identify and explore new directions in any field of research (Physical Sciences and Engineering, Life Sciences and Social Sciences and Humanities) with no thematic priorities. In particular, it encourages proposals which cross disciplinary boundaries; address new and emerging fields and introduce unconventional and innovative approaches.

Since 2007, the ERC has funded over 4,000 researchers. The ERC awards long-term grants to individual researchers of any nationality and age who wish to carry out their research projects in Europe. Excellence is the sole criterion for evaluation.

# Picturing cancer in 3D

Cancers affecting the stomach and intestines are among the most frequently occurring forms of the disease. Dr Danijela Vignjevic's ERC-funded project is investigating what happens to cells in the very early stages of colorectal cancer development. By advancing our knowledge of how colorectal cells work, the research could have future applications in producing drugs that target stromal cells, rather than cancer cells, in order to prevent the development of secondary malignant growths.

The entire lining of our intestines is renewed every week by cells multiplying and migrating towards the tips of the 'villi' – the finger-shaped protrusions that line the intestines and absorb nutrients from our food. Cancer may result when cells multiply more than usual, or do not die, or do not migrate enough or normally. This project intends firstly to enhance our understanding of precisely how these cells migrate and how normal gut tissue is renewed. The research group will then undertake detailed study of interactions between cancer and stromal cells during invasive migration.

This project is unusual for its focus on the cell biology at the initial stages of cancerous development, rather than on the later medical issues, but also for its methods of investigation. The project uses new 3D imaging technology to study the fundamental mechanisms of cell migration – both in cancerous invasion and in the normal function of the intestine. With the support of an ERC grant, the research group has been able to buy and operate a 'two-photon microscope', which takes images of cells buried deep inside tissue. This expensive equipment uses fluorescence to produce real-time images while inflicting less 'phototoxicity' damage to cells or tissue than comparative methods. The ERC grant has also made it possible for eight specialists to work on the project, which bridges several scientific fields.

Although the research is due to run until 2017, good progress has already been made in the study of how cancer cells break through the basement membrane to spread to other organs. By imaging intestinal cells over three days from birth to death, the project has also advanced understanding of cell migration.

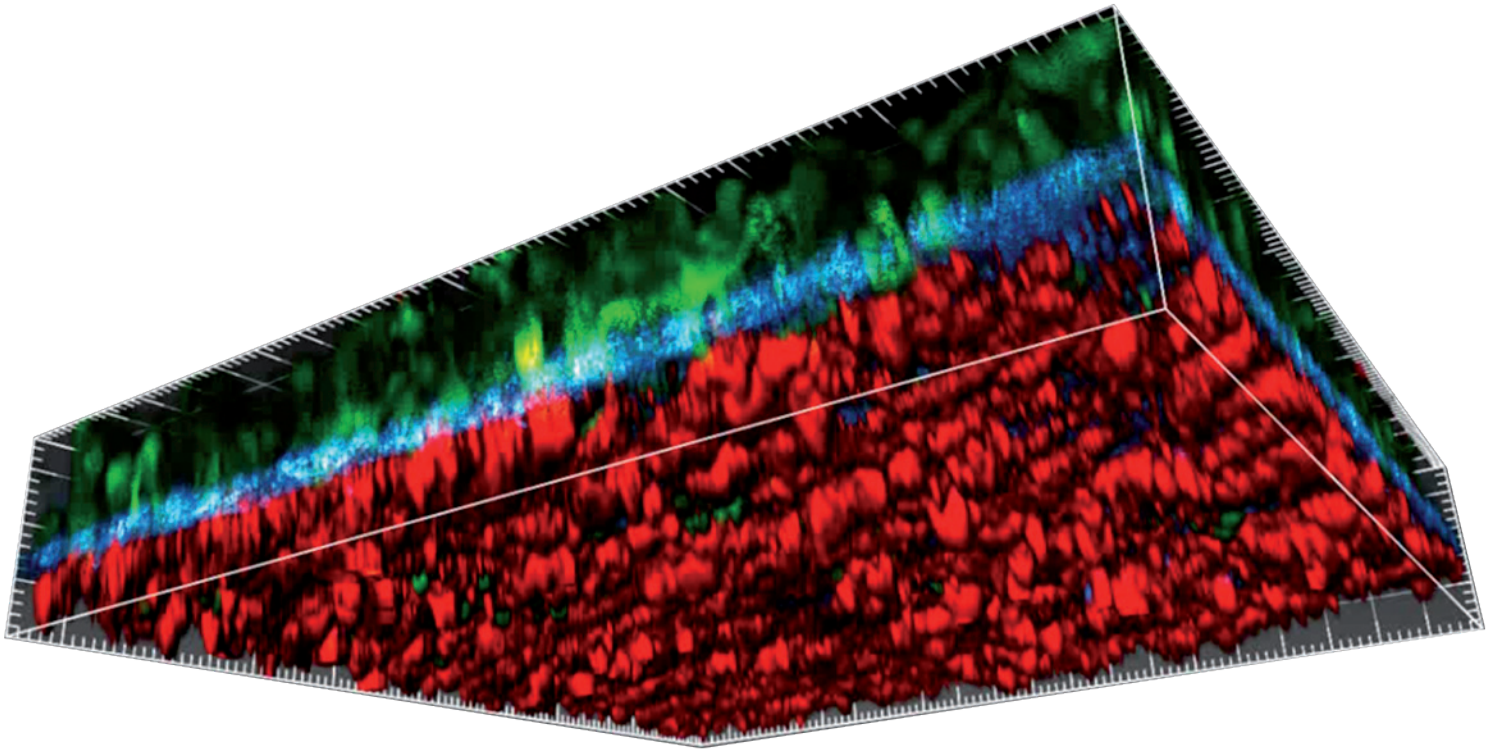
**Principal Investigator:** Dr Danijela Matic Vignjevic

**Host Institution:** Institut Curie (France)

**ERC Project:** Cell migration in gut homeostasis and cancer invasion - role of microenvironment (STARLIN)

**ERC call:** Starting Grant 2012

**ERC funding:** €1.5 million for five years



Cancer cells (green), cancer-associated fibroblasts (red), basement membrane (blue)

# The importance of detecting early tumour cells

Breast, prostate, lung and colorectal cancer are responsible for 90% of all new cancers in Europe. The technologies currently in use are not sufficiently sensitive to track a highly significant stage in a tumour's progress: the spread of early tumour cells. Prof. Klaus Pantel and his team have developed ultra-sensitive procedures which can detect single tumour cells in cancer patients' blood and bone marrow. This novel method enables clinicians to more accurately target therapies and to trace patients' resistance to therapeutic treatments. A network of collaborations with clinicians will allow the team to detect and characterise the blood and bone marrow of patients suffering from breast, prostate, lung and colorectal cancer.

The patients will be drawn from those taking part in clinical trials to ensure that there is a uniformity of treatment and clinical information. This investigation will be underpinned by an analysis of clinical practice in order to identify the diagnostic procedures and treatment modalities which have the greatest impact on the dissemination of tumour cells: tumour biopsy, surgery, radiotherapy, chemotherapy and targeted treatments for example.

Using state-of-the-art technologies, Prof. Pantel hopes to reach novel insights into the biological process by which tumour cells spread. Ultimately, it is expected that this will lead to the more efficient and effective management of cancer, and better treatments.

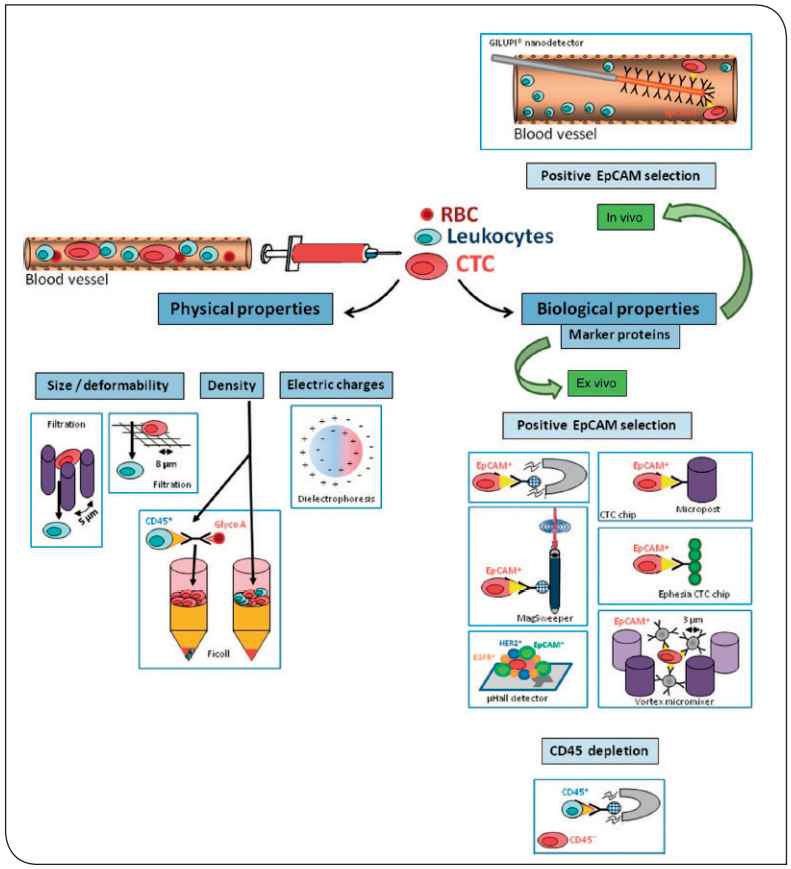
**Principal Investigator:** Prof. Klaus Pantel

**Host Institution:** Universitätsklinikum Hamburg-Eppendorf (Germany)

**ERC Project:** Disseminating tumour cells as novel biomarkers: Dissecting the metastatic cascade in cancer patients (DISSECT)

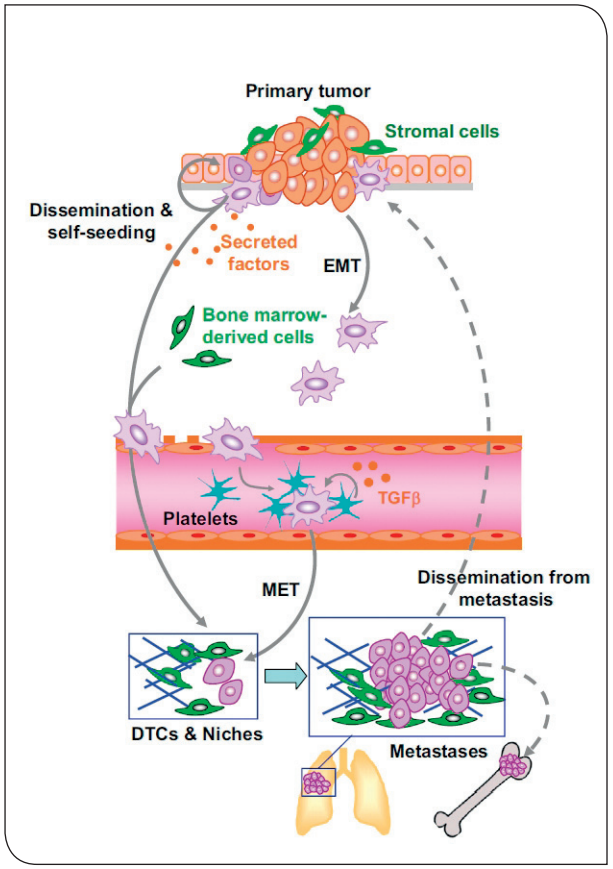
**ERC call:** Advanced Grant 2010

**ERC funding:** €2.5 million for five years






Enrichment of CTCs from the peripheral blood of cancer patients is based on the physical or biological properties of CTCs.






Dissemination, Survival, and Expansion of Metastatic Tumor Cells.

# Drug visualization to improve cancer treatments

Despite an abundance of drugs, cancer still remains a leading cause of death in developed countries. One of the major challenges for effective treatment has therefore become selection of the most promising new drugs. ERC grantee Prof. Elisabeth de Vries aims to create a drug development strategy which will facilitate more rapid, and smarter, clinical cancer drug trials.

Current drug development practices are slow, labour intensive, and also expensive. The new method of molecular imaging Prof. de Vries and her team are developing could help to characterize drug behaviour, improve drug targeting and produce better outcomes for patients. This approach has hardly been explored, which is mainly due to the radiation burden to patients caused by the radioactive tracers that are currently used in clinical research.

In the 'OnQview' project, Prof. de Vries proposes a radically different molecular imaging strategy based on using primarily non-radioactive methods. Her new approach involves optical and photo-acoustic imaging techniques: enabling scientists to visualize drug behaviour and tumour characteristics and then to track drugs and related proteins, called effect sensors. In this way, drug efficacy is measured in the early pre-clinical and clinical development stages of a drug, in contrast to current practice, where the effectiveness of a drug is assessed predominantly at the late-phase of clinical trials. The project focuses primarily on testing procedures for breast and colon cancer.

Prof. de Vries's research has great relevance for oncology, since it will allow dynamic treatment tuning in pre-clinical experiments and will guide patient-tailored selection of drugs. The multi-faceted character of this research is supported by a cross-disciplinary team of researchers.

**Principal Investigator:** Prof. Elisabeth de Vries

**Host Institution:** Academisch Ziekenhuis Groningen (The Netherlands)

**ERC Project:** Non-radioactive Molecular Imaging-Driven Drug Development in Oncology (OnQview)

**ERC call:** Advanced Grant 2011

**ERC funding:** €2.5 million for five years

# Remotely dispensed pain relief

Current treatments for those suffering chronic pain are often inadequate. In order to improve the daily lives of patients, a new drug delivery system is being developed by ERC grantee Dr Manuel Arruebo. The project could enhance the treatment of patients suffering from diabetes, hormonal disorders, sciatica, as well as those receiving localised chemotherapy treatments. This new technology would allow patients to benefit from a less invasive and more personalised method of drug dispensation – the device aims to implant nano-capsules capable of releasing drugs on-demand and remotely, removing the need for surgery in many cases.

A local injection of pain killers lasts for a short period of time and sustained treatments provide only a continuous nerve blockade. Pain management methods do not currently adapt to changes in patients' daily lives – the level of relief is the same during physical activity as at bedtime, for example. In addition, conventional systems do not allow the patients or their doctors to switch off drug delivery or administer therapeutic doses only for the length of time which is necessary.

Dr Arruebo's project, funded by the 4,000th ERC grant, intends to overcome these limitations by developing nanocapsules that can administer prescribed medication in a way that is consistent with the extent and duration of pain. With use of a secure locally-injected drug reservoir, close to the affected nerves, medication could be released remotely and on-demand, as and when required. The biocompatible drug loaded nanocapsules would be near infrared-sensitive and as such could be activated with use of a simple handheld laser device. Adjustable drug release profiles triggered remotely by patient or clinician would provide more flexible pain management and improve patients' quality of life considerably. Dr Arruebo and his team will design methods to synthesize these nanocapsules and load them with medication using "microfludic reactors", the design of which will be supported by Computational Fluid Dynamics (CFD) simulations.

This drug delivery system would surpass the current state of the art. There are presently no such remote drug delivery devices available to clinicians that do not require large and expensive equipment found exclusively in specialised hospitals. The pioneering technology developed in this project would be accessible at any point-of-care and could have subcutaneous, intraperitoneal, intramuscular, and transdermal applications.

**Principal Investigator:** Dr Manuel Arruebo Gordo

**Host Institution:** Universidad de Zaragoza (Spain)

**ERC Projects:** A Photo-triggered On-demand Drug Delivery System for Chronic Pain (NANOHEDONISM)

**ERC call:** Consolidator Grant 2013

**ERC funding:** €1.5 million for five years

NIR light is used for the triggered delivery of drugs

# Cancer and the length of your chromosomes

The answer to why some people age earlier than others, and why they develop cancer, could lie at the very end sections of our DNA: in the telomeres. In human cells, DNA is formed into chromosomes which have long sections of DNA at their ends, called telomeres. The main role of telomeres is to protect the ends of the chromosomes, just like the plastic ends of shoelaces. Each time a cell divides, the telomeres shorten. Without them, the main part of the chromosome containing our life-giving genes would become shorter, thus preventing our cells from functioning properly. Telomere shortening is known to be associated with cancer, ageing and loss of stem cell function.

The aim of the 'TEL STEM CELL' project was to determine the role of telomere length regulators (such as specific proteins and genes) in cancer, ageing and stem cell biology. For this purpose, normal mice were compared with "knockout" mice: genetically engineered mice that lack the particular gene which the project studies.

In 2009, Prof. Maria Blasco's team showed for the first time that a telomere-binding protein can suppress tumour formation and stop premature ageing of tissues. A gene called TRF1, which is enriched in stem cells, commands the production of a telomere binding protein and the research proved that mice without this gene aged quicker and were more prone to develop cancer. A year later similar functions were demonstrated for other telomere-binding proteins. TPP1, for example, was shown to play an essential role in telomere elongation by recruiting the protein telomerase to the chromosome ends.

Unexpectedly, Blasco's team also discovered that RAP1 - the most conserved telomere binding protein in evolution - is dispensable for telomere protection in mammals. Instead, the main function of RAP1 is to bind along chromosome arms and regulate gene expression. Blasco's group found that RAP1 is a key regulator of metabolism. Indeed, mice with no expression of RAP1 were obese and developed signs of metabolic syndrome. This has opened an unprecedented link between telomeres and metabolism.

In order to better identify the role played by stem cells in ageing and cancer, Blasco has succeeded in generating mice deficient in the "Tin2" regulator, which can cause diseases such as aplastic anemia and pulmonary fibrosis. The group is studying the role of Tin2 in disease as well as its potential as a therapeutic target.

**Principal Investigator:** Prof. Maria Blasco

**Host Institution:** Fundación Centro Nacional de Investigaciones Oncológicas (Spain)

**ERC Project:** From telomere chromatin to stem cell biology (TEL STEM CELL)

**ERC call:** Advanced Grant 2008

**ERC funding:** €2 million for five years

# What healthy breast tissue can teach us about breast cancer

Globally, breast cancer is the most common cancer amongst women. In 2012, almost 1.7 million women were diagnosed with breast cancer, a figure which accounts for 25% of cancer cases amongst women. The contention driving this ERC-funded research is that scientists still do not know enough to explain why some patients respond well to therapeutic treatments, whilst others continue to decline.

Breast tumour biology still remains relatively opaque – very little is known about the pathways and molecules involved for example. Expanding this knowledge is critical because breast cancer subverts the majority of the signalling pathways which control healthy breast development. If we understand more about how these pathways work then we can illuminate the role of cancer cells in throwing them off course. Dr Mohamed Bentires-Alj and his team hope to point the way to more effective treatments through their understanding of the biology of healthy breast development and cancer progression.

The 'PTPsBDC' project is studying the role of protein-tyrosine phosphatases (PTPs) in both normal breast development and cancerous tissue. This research is innovative because it crosses the boundaries between developmental and cancer research fields, and between basic science and clinical applications. It is hoped that the knowledge generated in the course of this project will form the foundation for prognostic/predictive markers. These could lead to the development of more effectively targeted therapies for breast cancer patients.

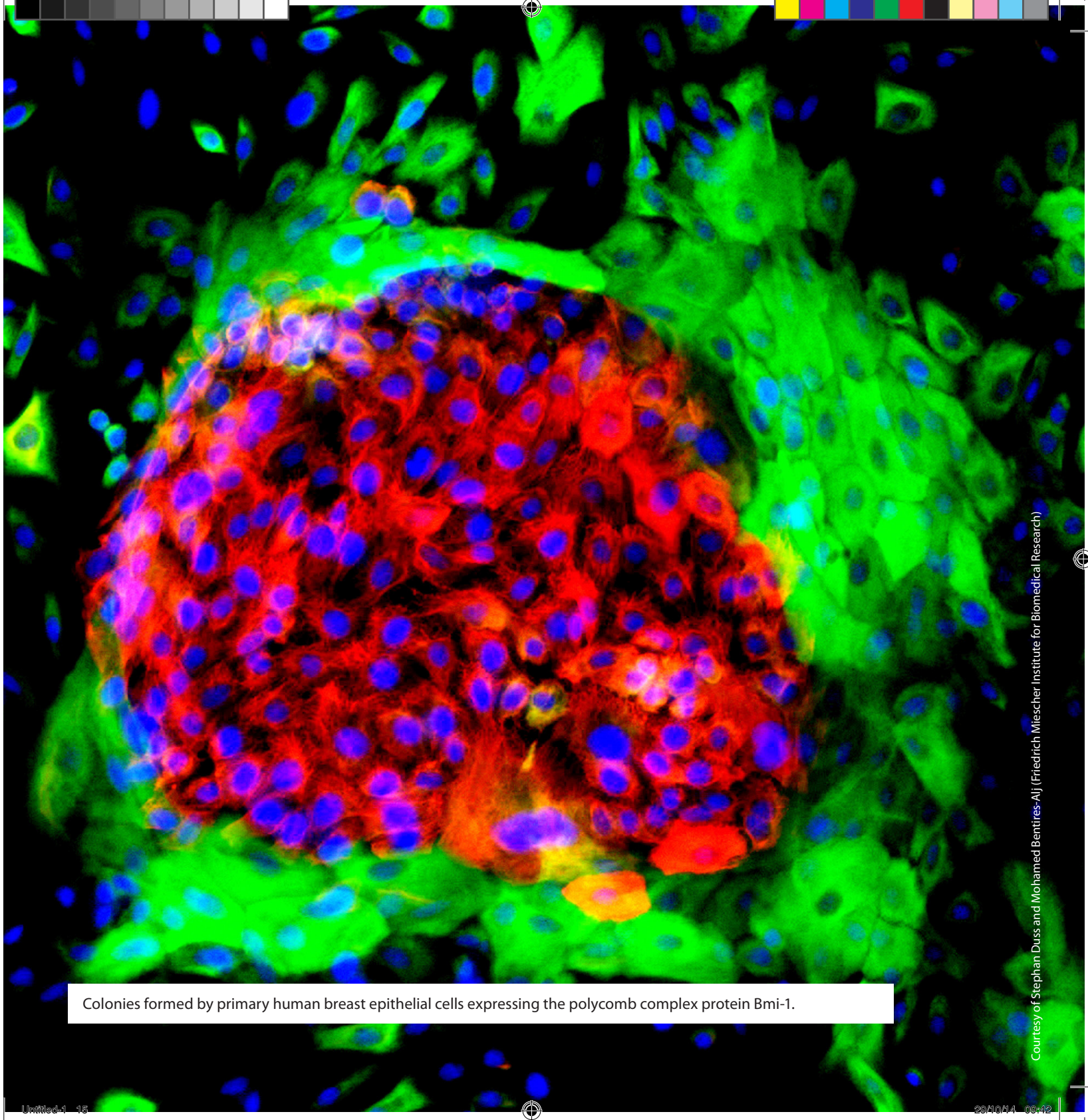
**Principal Investigator:** Dr Mohamed Bentires-Alj

**Host Institution:** Friedrich Miescher Institute for Biomedical Research, Basel (Switzerland)

**ERC Project:** The role of protein-tyrosine phosphatases in breast development and cancer (PTPsBDC)

**ERC call:** Starting Grant 2009

**ERC funding:** €1.6 million for five years



Colonies formed by primary human breast epithelial cells expressing the polycomb complex protein Bmi-1.

Courtesy of Stephan Duss and Mohamed Bentires-Alj (Friedrich Miescher Institute for Biomedical Research)

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Jean-Pierre Bourguignon
ERC President and Chair of its Scientific Council

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