Systems biology: shaping the future of breast cancer treatment

Professors Robert Coleman and Philippe Bedard lift the veil on the conference programme.

You can make a difference!
Take action.
The first BIG Garden Party and other ways to support breast cancer research.

IMPAKT 2016 - Your first meet & greet with the co-Chairs
Professors Robert Coleman and Philippe Bedard lift the veil on the conference programme.

Together we can do more
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In our fight against breast cancer we have made tremendous progress in getting to know our enemy. For several years now cancer research has entered the era of *Precision Medicine*. Researchers have at their disposal ever-more sophisticated technologies to dissect tumours and to identify their specific molecular characteristics. Based on the biology of cancer, current clinical trials try to match novel targeted drugs with the molecular aberrations found in a patient’s tumour. We now understand that each tumour is unique. However, the deeper we dig into tumour heterogeneity, the more complex we find the battlefield.

How is it possible to identify the specific molecular aberrations that cause and maintain each patient’s tumour? How can we predict the functional effects of a drug in the cancer cell? How can we understand in depth the intracellular changes and interactions that drive cancer, the behaviour of a cell within a tumour and in the larger physiological ecosystem of the patient? How, among the thousands of possible combinations of targeted drugs, will we find the most appropriate and logical one that will lead to cancer cell death? At the end of the day, how can we predict which treatment strategy will work best for each individual patient?

In this context, we believe that the systems biology approach will play a critical role in the future. Mathematical modelling can enable us to predict what our eyes cannot see.

Involved in the huge challenge to master systems biology techniques and to translate them into the clinic are biological scientists, mathematicians and clinicians from both sides of the Atlantic. For this issue of *Research in Focus*, we recently asked Professors Gordon Mills (University of Texas MD Anderson Cancer Center, USA), David Cameron (Edinburgh Cancer Research Centre, UK), Andrea Califano (Columbia University, USA) and Christopher Lord (Institute of Cancer Research, UK) to tell us more about this integrated approach that we hope will guide researchers towards more rational clinical testing, better treatment strategies and more effective cures for patients.

In addition, you can look forward to reading an interview with the Co-Chairs of the 2016 IMPAKT breast cancer conference on translational research, Philippe Bedard and Robert Coleman, who lift the veil on its very exciting programme.

I hope you enjoy the reading.

Martine Piccart-Gebhart
Breast International Group (BIG) Chair
By Jenny Bryan

Systems biology involves building mathematically based models of the functional consequences of changes to intracellular networks that occur during or after carcinogenesis – not only in isolation, but also within the context of the local microenvironment and the larger physiological ecosystem. In breast cancer, as in many other forms of the disease, the systems biology approach is expected to pay dividends in shaping rational combinations of targeted drug therapies and predicting patient response to treatment. Jenny Bryan reports research and clinical perspectives on the potential of systems biology for future advances in breast cancer care.

Building a complete picture of the most important genetic mutations and abnormal protein behaviour in a cancer cell within the broader physiological ecosystem and predicting the likely impact of drug interventions sounds like mission impossible. But a powerful coalition of biological scientists, mathematicians and clinicians has not only accepted the challenge, but is well on the way to completing the mammoth task.

Essential to the success of the mission is the bringing together of a number of cutting edge biological and computational technologies that facilitate the collection and analysis of huge
Systems biology is going to play an absolutely critical role in how we combine targeted therapies rationally and with immunotherapies to give us a more efficient way of moving forward, instead of trying every two-by-two combination we can think of, without predicting who is likely to benefit.

Professor Gordon Mills, who started the first department of cancer systems biology at the University of Texas MD Anderson Cancer Center in Houston, USA, predicts that the rational use of systems biology will have a major impact in identifying better ways of treating patients with cancer: “Having spent 20 years trying to draw arrows in signalling pathways, I realised that those arrows, though important, did not explain how the system worked in context and that we needed a new approach. Systems biology is going to play an absolutely critical role in how we combine targeted therapies rationally and with immunotherapies to give us a more efficient way of moving forward, instead of trying every two-by-two combination we can think of, without predicting who is likely to benefit.”

As a clinician currently using predictive tests for breast cancer treatment based on mutations in up to 70 individual genes, Professor David Cameron, Clinical Director and Chair of Oncology at the Edinburgh Cancer Research Centre, in Edinburgh, UK, and member of BIG’s Executive Board, welcomes the potential for the more integrated approach offered by systems biology.

“The new technologies are revealing much more information about what is going on in cancer cells and how the cancer interacts with the patient, though we are not yet at the point of using the constructs generated by systems biology in the clinic. But I am hoping that, in perhaps five years, we will be able to compare test results in our patients with known biological insights and algorithms generated by systems biology to understand what is happening in each patient’s tumour,” says Professor Cameron.

Like Professor Mills, he hopes that systems biology will enable new drug combinations to get to the clinic more quickly, thanks to faster, more logical clinical testing.

“We have enough different drugs coming through, targeting different pathways, to be able to construct the drug combinations we need to tackle cancer biology but if we put them together randomly we’ll have potentially thousands of..."
combinations to get through,” says Professor Cameron. “Hopefully, systems biology will allow us to combine drugs more logically and rapidly, based on a better understanding not only of how the cancer is behaving before we started treating it, but also how it has adapted to the treatment we’ve already given.”

Identifying driver mutations
Most genetic mutation patterns that produce cancer have not been observed – and never will be – because they are largely unique to the individual patient. So it is essential for systems biologists to identify the driver mutations that impact cancer cell signalling rather than the passenger mutations that are largely irrelevant.

Professor Andrea Califano, Chair of the Department of Systems Biology at Columbia University, New York, USA, points out that the number of possible mutation patterns lies somewhere between $10^{20}$ and $10^{50}$, so there aren’t enough cells, let alone patients, on the planet to be able to investigate all the different patterns of mutations that can cause cancer:

“Some patterns are more frequent but once we get beyond the 60 or 70 genes that play a dominant role in tumorigenesis, the contribution of the others becomes essentially invisible on a gene by gene basis. This is why we need to model what we can’t see.”

Professor Califano highlights the importance of so-called master regulator genes, or tumour checkpoints that are rarely mutated themselves but act as a downstream “funnel”, through which aberrant signals generated by large numbers of mutated genes must pass.

“At the gene level, regulator genes do not have mutations, are not differentially expressed and are difficult to understand but they are incredibly relevant for maintaining the tumour state,” he says.

Hitting the products of master regulator genes downstream of many different genetic mutations has potential not only for primary treatment but also in limiting the ways that a tumour can relapse. For example, a tumour may be largely dependent on PI3 kinase (PI3K) mutations for growth but a few cells may be dependent on PTEN deletions. Knock out the PI3K pathway, and the cells with PTEN deletions can still take over to sustain tumour growth. However, acting downstream of both potential mutations will ensure full tumour inhibition.

“It doesn’t mean that a tumour can’t re-programme itself into a different lineage, with different master regulators. We may need to treat a cancer as several different types of tumour, but at least that is better than trying to address the huge number of potential mutations that may be present and will almost certainly allow resistance to occur,” says Dr Califano.

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but whether it is aberrantly active. There are many
different reasons why proteins such as ER may be
aberrantly activated, such as mutation of one of
the receptor regulators or deletion of a sequence
of suppressor microRNA. But only if it is activated
will drugs such as tamoxifen be effective.

Similarly, by establishing the profile of target
genes whose expression is upregulated or re-
pressed by the epidermal growth factor receptor
(EGFR), an established cancer driver protein, it is
possible to predict what a tumour with activated
EGFR might look like. By testing tumour samples
for how EGFR target genes are differentially ex-
pressed, it is possible to establish whether the
patient has an activated EGFR or whether it is bet-
ter to move on to another potential driver protein.

“We can literally go protein by protein and draw
up a list for each patient of those that are aber-
rantly activated. Then we can try to match them
with a list of drugs that can shut them down,”
says Dr Califano.

He reports that he and his team have recently
identified aberrantly activated proteins that are
never mutated in breast cancer and yet are re-
sponsible for resistance to trastuzumab in pa-
tients with HER2 amplified breast cancer. Based
on these findings, a multi-institutional clinical trial
using a combination of trastuzumab and ruxol-
itinib to target both HER2 and these aberrantly
activated proteins is currently enrolling patients,
with the corresponding manuscript just accepted
for publication in Genes and Development. Initial
data look very promising, with two patients who
had progressed on other therapies showing sta-
ble disease for 11 weeks and significant improve-
ment of skin lesions.

Using systems biology to create the extensive
data bases of driver protein profiles against
which drugs can be matched is a massive un-
dertaking. But each new piece in the picture
moves breast and other cancer patients closer to
the day of routine, personalised care.

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operate in breast
cancer, we can start
to come up with
novel therapeutic
approaches.

Dr Lord

He and colleagues have shown that a relatively
small number of 10-20 master regulator genes
are involved in the survival of tumours in breast
cancer patients. Of these, oestrogen and proges-
terone receptor (ER and PR) genes and GATA 3
are mutated, but most of the others are not.

“We’ve found that, while it is very difficult to find
a single gene that drives a cancer, we can find
two or three genes that synergistically drive the
tumour. Activation of these individual genes does
nothing, but coactivation of multiple genes can
result in a very aggressive tumour,” he says.

Dr Califano points out that identifying driver mu-
tations is only part of the puzzle; finding out which
proteins are activated that control tumour main-
tenance is at least as important. He explains that
it is now possible to measure the activity of im-
portant driver proteins in cancer according to the
expression of their targets.

Dr Califano says that identifying the targets for
each protein in the cell – a process called reverse
engineering the regulatory logic of the cell – is
a huge challenge for researchers, not least be-
cause the “logic” is very different from cell to cell
and patient to patient. However, improvements
in the algorithms used in the reverse engineering
process have helped to streamline understand-
ing of the protein targets and to construct models
of how different cells and tissues are regulated.

For example, a woman may be classified with lu-
minal breast cancer but that does not mean she
will respond to ER inhibitors. What matters, as Dr
Califano explains, is not that the ER is amplified

The importance of synthetic lethality
Armed with the results of over a decade of re-
search that has identified the main molecular
changes associated with breast cancer, Dr Chris-
topher Lord and colleagues in the Gene Function
Team at the Institute of Cancer Research (ICR),
London, UK, are searching for therapeutic targets
for key driver events.

They are using high throughput screening to
demonstrate the functional effects of perturbing
relevant genes in breast cancer and, in particu-
lar, the synthetic lethal effects arising from combinations of gene mutations that would not individually lead to cell death but could prove fatal when they occur together.

“If human cells are anything like yeast cells, where there are somewhere in the region of 10-100 synthetic lethal interactions for every gene, we have the chance to identify synthetic lethal interactions for many of the genes that drive breast cancer. If we can understand the synthetic lethal interactions that operate in breast cancer, we can start to come up with novel therapeutic approaches,” explains Dr Lord.

Identification of the synthetic lethal interaction between inhibitors of poly(ADP-ribose) polymerase (PARP) and BRCA1 and BRCA2 genes by the ICR team led to the development of a PARP inhibitor-based therapeutic strategy for the treatment of BRCA mutated ovarian cancer. Inhibition of PARP, an enzyme involved in repair of single strand breaks in DNA is not normally fatal to cells. But in the absence of normal BRCA gene function essential for repair of double strand breaks in DNA, inhibition of PARP activity leads to persistence of DNA damage in cancer cells and ultimately to cell death.

“We are still learning how best to use PARP inhibitors in breast cancer, so that we take account of the potential for the emergence of drug resistance. This is building on our understanding of synthetic lethality, and helping us move towards our goal of developing the maximum number of treatment options for any given patient,” says Dr Lord.

Breast cancer research is also focusing on synthetic lethality due to interactions around defects in the PTEN tumour suppressor gene, and other commonly mutated breast cancer genes, such as p53, PIK3CA and ERBB2.

“At a mutational level, breast cancer is very heterogeneous, with many mutated genes in relatively small fractions. So we’re going after mutations that are relatively common and where we have practical ways to pursue them,” says Dr Lord.

Essential to such advances in understanding of how synthetic lethality can be exploited for novel targeted therapies have been important developments in high throughput gene profiling and perturbation technologies.

Dr Lord explains that, for some time, small interfering RNA (siRNA) screens have been used systematically to perturb large numbers of genes and look for the effects on cellular phenotypes. More recently transposon-based mutagenesis and CRISPR-based mutagenesis and CRISPR-based interference have also been used to modulate genes and observe the effects on cells.

“It’s called high throughput screening, but that doesn’t necessarily mean it’s fast. There is a huge logistic investment in setting up such platforms and physically doing the screens and analysing the data,” says Dr Lord. “Some of these technologies take years to refine in any individual lab. We’re getting to the stage where people can compare different datasets from different groups, but we still have a long way to go. We want to understand whether an observation in one cell line is peculiar to that cell line or is a generalisable observation, and that requires significant validation. We can’t just make an observation and jump straight into a clinical trial.”

The power of maths

Systems biology is an information intensive science, and mathematical modelling using computational biology, bioinformatics and statistical analysis is an integral part of this approach.

Professor Mills explains that just as mathematical modelling enabled physicists to predict the presence of subatomic particles before they were actually found, emergent information from modelling in systems biology is guiding researchers towards the pathways on which they should be focusing and helping to predict what was previously unknown.

“If we build a mathematical model of a process in a cell and the maths doesn’t add up, that means there are pieces of information we are missing. If we build a biological pathway and we don’t get the answer we expect when we perturb it, it’s possible there’s something wrong with the maths, but usually it’s because we are missing important components of the pathway that we need to look for, such as a feed-forward or a feedback loop,” says Professor Mills.

He describes how maths-intensive modelling can also be used to establish just how big a perturbation in enzyme activity in a pathway is needed to alter cell behaviour. For example, it is well established that mutations in the AKT oncogene drive cancer, but mathematical modelling has predicted that an 80-90% change in AKT enzyme activity would be needed for a significant change in cell behaviour – something which has been confirmed in vitro and clinically.
Thus, mathematical modelling has shown that AKT is present in massive excess. So unless its activity is markedly compromised, there will be limited effect on cancer cells.

“This has turned out to be a major problem in cancer patients because we do not have a sufficient therapeutic index with our drugs targeting the AKT/PI3K pathway to have the marked therapeutic impact we expected. If we had paid more attention to the maths, we wouldn’t have treated patients with drugs that were not as effective as we had hoped,” says Professor Mills. “We now know that maths can tell us an enormous amount about how to knock out a pathway in order to have a marked effect on cell biology.”

A role for N=1 studies?
By enabling clinicians to match a patient’s driver mutations and cancer cell behaviour to the most appropriate combination of targeted therapies, systems biology will provide an important stepping stone towards personalised cancer therapy. But evaluating all the possible treatment permutations in conventional clinical trials will be a massive undertaking. In the meantime, some systems biologists, such as Dr Andrea Califano, are testing established and investigational cancer drugs in N=1 studies of patients with well-defined driver mutations.

One such study is focusing on 260 patients across nine rare or untreatable cancers, including metastatic, mainly triple negative, breast cancer, in which a tumour sample from a patient is transplanted into an immunocompromised mouse. Computational modelling is used to predict the vulnerability of the tumour to different doses of a number of targeted agents, both as single and combination treatment, and these are then tested in vitro before the most promising candidate is tested on the mouse. If beneficial effects are seen in the xenograft, treating physicians are informed of the results so they have the option of offering the same treatment to the patient.

“We are prioritising about 1500 FDA approved drugs and late stage investigational agents and, although it will be a year or 18 months before we have results, we hope that anecdotal information will be available before that,” says Dr Califano.

N=1 studies have the advantage of rapid testing and the opportunity for highly personalised treatment for the patient – assuming that an agent is available that targets their particular profile. Dr Califano’s studies will begin to answer questions over whether responses seen in xenografts are repeated in patients. But, as with any treatment based on biopsy material, there is no guarantee that the N=1 approach will define a therapy that will be effective against all the cancer cells in a patient’s body. Nor will such studies show how treatment compares with standard of care. Can N=1 studies achieve sufficient statistical rigour for them to be used more widely than in phase 1 studies for patients who have failed all other therapies?

Dr Califano accepts that promising results from N=1 studies will not be enough to convince regulators to licence new drugs but says that they will become the basis to run more conventional clinical trials with much larger numbers of patients, based on master regulator activity. He suggests that targeting master regulator genes that are conserved and critically important for tumour growth in large numbers of patients will be much more appealing to pharmaceutical companies and regulatory bodies than addressing individual mutations that are detected in a much smaller number of patients.
“The discovery part requires N=1 studies but when we’ve identified the commonalities, we can target much larger subsets of patients with breast cancer, for example, with the same drug. So it’s not just precision medicine at the individual level, but for much larger populations,” he concludes.

Translating systems biology into clinical practice

Enthusiasts for systems biology are eager to convince their clinical colleagues of its value in helping to select patients who are most likely to benefit from targeted therapies and for the development and introduction of rational drug combinations.

Professor Mills suggests that the excitement around systems biology focuses on **three key concepts:**

- the ability to predict processes in the cell that can then be investigated experimentally
- the opportunity to understand the level of target inhibition that is required to achieve a therapeutic effect
- the facility to identify compensatory mechanisms in the cell in order to optimise the way that combinations of targeted therapies are administered

“For breast cancer, we already have a greater treasure trove of information around these key concepts than for any other disease. However, breast cancer is complicated by the fact that it is, in effect, made up of many independent, biologically separate diseases. We therefore need enough information about each of them to predict the functional consequences of our therapeutic approaches in order to make the right treatment choices,” says Professor Mills.

As dysregulation of the PI3K pathway is so prominent in breast cancer, systems biologists are focusing heavily on what happens when various elements of the pathway are activated or bypassed.

“We and others have shown that, if one node in the pathway is inhibited, others become highly activated as potential bypass mechanisms, so these additional nodes need to be targeted if we’re going to have effective outcomes in patients,” says Professor Mills.

Preclinical research has identified and demonstrated efficacy of novel compounds against targets of PI3K bypass mechanisms, such as Bcl2 and BCLXL, and clinical studies are planned.

Already on trial in breast cancer clinics are combinations of PI3K inhibitors and PARP inhibitors, which, systems biology has shown, have complementary effects on the compensatory mechanisms activated in cancer cells when each type of inhibitor is used separately.

“We’re already seeing striking responses in a number of patients and the question will be whether we can find biomarkers to identify those who will benefit most. We also need to work out which node in the PI3K pathway we need to target for each patient to get the best results when we combine treatment with PARP inhibitors or other agents,” explains Professor Mills.
Breast cancer specialists such as Professor Cameron see obvious advantages to combining therapies that target primary and resistance mechanisms from the outset, rather than waiting for resistance to emerge.

“We have been improving cure rates for breast cancer for the last 30-40 years, but each time we come up with a new drug or drug class that makes a difference, we still get resistance. If systems biology can predict which biological pathways will drive resistance in certain patients, that will help us pre-empt the effects of those resistance mechanisms in our treatment strategies,” he says.

While few clinicians would argue with the personalised medicine approach that systems biology aims to achieve, there is some scepticism about whether it can deliver where so many previous approaches have failed.

Professor Cameron points out that there is an inherent cynicism about an algorithmic “black box” approach to medicine, but agrees the need for systems biology to integrate information about what happens in cancer cells into the overall clinical picture.

“It’s a big and complex step to go from what the clever scientist tells you happens in systems biology to what the clinician sees as a credible recommendation. Systems biology is a very important approach, but any treatment recommendation will need to be based on clinical trials demonstrating superiority over standard treatment and will also need to make intrinsic sense. I don’t think anyone is expecting to suddenly get a magic combination for each patient, with cures for everybody. But iterative progress in dealing with resistance as it emerges – or is predicted to emerge – would represent a very worthwhile advance in the way we treat breast cancer.”

Further reading


Meet the experts

Andrea Califano, Dr
Clyde and Helen Wu Professor of Chemical and Systems Biology
Chair, Department of Systems Biology
Director, JP Sulzerber Columbia Genome Center
Associate Director, Herbert Irving Comprehensive Cancer Center, Columbia University, New York, (NY) USA

David Cameron, MD
Professor of Oncology, University of Edinburgh & Director of Cancer Services, NHS Lothian
BIG Executive Board member

Christopher Lord, PhD
Leader, Gene Function Team and Reader in Cancer Genomics and Therapeutics, The Institute of Cancer Research, London, UK

Gordon Mills, MD, PhD
Chair and Professor, Department of Systems Biology
Professor of Medicine and Immunology, University of Texas MD Anderson Cancer Center, Houston (TX), USA
Looking forward to the IMPAKT 2016 Breast Cancer Conference

More than 500 oncologists and other experts are expected to gather in Brussels from 12 to 14 May 2016 at the 8th IMPAKT Breast Cancer Conference to hear about the latest advances in translational research and to discuss implications for clinical research and patient care.

The IMPAKT 2016 co-chairs Philippe Bedard and Robert Coleman tell us why it is worth attending.

What’s new in the 2016 scientific programme, in comparison to the past editions?
The 2016 programme will provide the latest information on important areas of translational science and how these developments are best integrated into clinical practice. A variety of formats – including case based discussions on how to integrate genomic information into patient care, multi-professional discussions on trial design from academic, industry and regulatory standpoints as well as keynote lectures, interactive poster sessions and structured discussion of key topics – are designed to bridge the gap between science and the clinic even more effectively than previous meetings.

The opening day will highlight advances in immunotherapy and emerging combinations of immunodulatory approaches that can be applied to breast cancer. The second day will feature mutational and epigenetic characterisation of endocrine dependent cancers, emerging novel targeted therapies, and a roundtable discussion of the challenges of breast cancer clinical trials in the era of increasing genomic fragmentation. The third day will profile novel antibody-drug conjugates, exciting advances in circulating technologies to monitor therapeutic response and minimal residual disease, and the conference will conclude with a multi-disciplinary “genomic tumour board” with a case-based discussion of the opportunities and challenges of multi-gene sequencing in clinical practice.

Dr Bedard is an Assistant Professor of Medicine at the University of Toronto. He is a Staff Medical Oncologist in the Division of Medical Oncology and the Fellowship Director for the Bras Family New Drug Development Program at the Princess Margaret Cancer Centre, Toronto, Canada. He received his medical degree from the University of Toronto where he was awarded the Cody Academic Silver Medal. He completed his Internal Medicine and Medical Oncology specialty training at the Breast International Group (BIG).

Since 2014, he has been a part-time Medical Director for the independent medical education provider, priME Oncology™ alongside his ongoing role within the university. He is passionate about improving the care of cancer patients through research and has particular interests in new developments in the management of breast cancer and the effects of cancer and its various treatments on the bones. He has written more than 400 scientific articles and book chapters and leads a number of national and international clinical trials.

Professor Robert Coleman is the Yorkshire Cancer Research Professor of Medical Oncology and Honorary Consultant in the Academic Unit of Clinical Oncology at Weston Park Hospital, Sheffield, UK. He graduated in medicine from Kings College Hospital Medical School in 1978 and trained in London and Edinburgh before moving to Sheffield in 1991. For more than 20 years, he has been instrumental in developing clinical cancer research in the city and surrounding clinical network. During that time, he has held many leadership roles within the local university, the NIHR Cancer Research Network and the NCRI.

The Conquer Cancer Foundation of the American Society of Clinical Oncology recognised him with a 2012 Career Development Award. His clinical practice includes the treatment of patients with breast and testicular cancers. As the Clinical Director for the Cancer Genomics Program at the Princess Margaret Cancer Centre, his research involves early phase clinical trials and the personalisation of cancer treatment based upon the results of testing for DNA mutations within tumour cells.
The keynote lecture will address cancer immunotherapy: why is this an important topic in breast cancer today and what can we expect to learn?

Immune modulation via various immunotherapy strategies is rapidly transforming the management of a wide range of cancer types. However, the potential relevance of the immune system in breast cancer has been recognised only relatively recently and we are only just beginning to see data emerging with the checkpoint inhibitors and other therapeutic strategies in breast cancer. However, there is much on-going activity in this area and IMPAKT will provide an opportunity to hear the latest developments as well as the chance to learn from the experiences of researchers involved in development of immunotherapy for other tumour types.

In particular, this keynote address will highlight the successes observed in other cancer types and the opportunities for therapeutic advances with immune oncology agents and drug combinations in breast cancer.

How is IMPAKT different from other breast cancer conferences, and who can benefit from attending?

IMPAKT is the only breast cancer conference specifically designed to translate scientific knowledge into the clinic and challenge both world leading scientific and clinical experts in the field to make the latest developments relevant and understandable. This meeting is a must for any clinician or scientist involved in breast cancer research wishing to understand the emerging science and make an impact on the future management of patients with breast cancer.

In addition, this meeting provides wonderful opportunities for early career researchers to advance their knowledge and skills through the pre-IMPAKT training course, to present their research, and to interact with key leaders in the field of breast cancer.

What do you make of your experience so far as international co-chairs of IMPAKT?

Robert Coleman: It is a privilege to be one of the co-chairs for IMPAKT and have the opportunity to bring together leading scientists and clinicians from around the world to this interactive meeting and work with the IMPAKT Executive to hopefully make the 2016 meeting the best yet.

Philippe Bedard: It has been a wonderful experience working closely with Rob Coleman, the Scientific Committee, and the IMPAKT conference organising staff to develop an exciting 2016 IMPAKT scientific programme. This meeting promises to build upon the energy and enthusiasm of past conferences to deliver the best IMPAKT meeting yet!
IMPROVING CARE AND KNOWLEDGE THROUGH TRANSLATIONAL RESEARCH IN BREAST CANCER

12-14 MAY 2016
Brussels, Belgium

IMPAKT CHAIRS
Robert Coleman,
Sheffield, UK
Philippe Bedard,
Toronto, ON, Canada

Conference Founders: José Baselga, New York, NY, USA and Martine Piccart, Brussels, Belgium

8th IMPAKT MAIN THEMES

- Checkpoints, immuno stimulatory molecules, combinations, and other immune approaches
- Molecular characterisation of endocrine dependent tumours
- New therapeutic strategies in ER positive breast cancer
- Novel drugs on the horizon
- Liquid biopsies
- Multidisciplinary genomic tumour board: Applying next generation DNA sequencing to clinical care

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Our vision: **We will find a cure for breast cancer through global research and collaboration**

The Breast International Group (BIG) is a non-profit organisation for academic breast cancer research groups from around the world.

Founded by leading European breast cancer experts in 1999, BIG now constitutes a network of 56 groups and data centres based in Europe, Canada, Latin America, the Middle East, Asia and Australasia. These entities are tied to several thousand specialised hospitals and research centres worldwide. About 30 clinical trials and several research programmes are run or are under development under the BIG umbrella at any one time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, so that together they act as a strong interacting force in the breast cancer research arena.

www.BIGagainstbreastcancer.org

### The 56 breast cancer research groups of the BIG network

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<td>Hellenic Breast Surgical Society</td>
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<tr>
<td>HeCoG</td>
<td>Hellenic Cooperative Oncology Group</td>
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<tr>
<td>HKBGG</td>
<td>Hong Kong Breast Oncology Group</td>
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<td>HOICG</td>
<td>Hellenic Oncology Research Group</td>
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<tr>
<td>IBCG</td>
<td>Icelandic Breast Cancer Group</td>
</tr>
<tr>
<td>IBCSG</td>
<td>International Breast Cancer Study Group</td>
</tr>
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<td>IBCG</td>
<td>Israeli Breast Group</td>
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<td>IBIS</td>
<td>International Breast Cancer Intervention Studies</td>
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<tr>
<td>ICCG</td>
<td>International Collaborative Cancer Group</td>
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<tr>
<td>ICN ARO</td>
<td>Indian Co-Operative Oncology Network</td>
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<td>ICORG</td>
<td>All Ireland Cooperative Oncology Research Group</td>
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<td>ICRC</td>
<td>Iranian Cancer Research Center</td>
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<tr>
<td>ICRI-CTSU</td>
<td>Institute of Cancer Research – Clinical Trials &amp; Statistics Unit</td>
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<td>IOSG</td>
<td>Indian Oncology Study Group</td>
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<td>ITMO</td>
<td>Italian Trials in Medical Oncology</td>
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<td>JBCRG</td>
<td>Japan Breast Cancer Research Group</td>
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<td>LACOG</td>
<td>Latin American Cooperative Oncology Group</td>
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<td>MICHIEANGELO</td>
<td>Fondazione Michelangelo</td>
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<td>NBCG</td>
<td>Norwegian Breast Cancer Group</td>
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<td>NCIC CTG</td>
<td>National Clinical Trials Group</td>
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<td>NCRI-BCSG</td>
<td>National Cancer Research Institute - Breast Cancer Clinical Studies Group</td>
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<td>SABO</td>
<td>Swedish Association of Breast Oncologists</td>
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<td>SAKK</td>
<td>Swiss Group for Clinical Cancer Research</td>
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<td>SBCG</td>
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<td>SwbBCG</td>
<td>Swedish Breast Cancer Group</td>
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<td>SKMCH &amp; RC</td>
<td>Shaukat Khanum Memorial Cancer Hospital &amp; Research Centre</td>
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<td>SLO</td>
<td>Société Luxembourgeoise d’Oncologie</td>
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<td>SOLOI</td>
<td>SUCCESS Study Group</td>
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<td>TCOG</td>
<td>Taiwan Cooperative Oncology Group</td>
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<td>TROG</td>
<td>Trans Tasman Radiation Oncology Group</td>
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<td>UCBG</td>
<td>Unicancer Breast Group</td>
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<tr>
<td>WSG</td>
<td>Westdeutsche Studiengruppe</td>
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</tbody>
</table>
Together we can do more

SAVE THE DATE!

- 4 October 2015
  BIG Garden Party
  Launch of the crowdfunding campaign in support to BIG Time for Baby: Pregnancy after breast cancer
  www.BIGtimeforbaby.org

- 30 November 2015
  Designers Christmas Trees – 3rd Belgian edition

And more events to come: check www.BIGagainstbreastcancer.org/events

How to help, if you are a …

**Company / Organisation**
Set up a “Look and Feel” health workshop at your workplace
BIG staff can present our “Look and Feel” guide to your employees, to raise awareness of breast cancer and promote early detection, for the well-being of your colleagues and their families.

**Collector / Art Aficionado**
Attend the prestigious “Belgian Designers Christmas Trees” event in Brussels
You can support BIG by taking part in the auction of unique pieces created by internationally renowned designers.

Or host an event to donate an artwork from your own collection for auction to benefit BIG.

**Community Leader**
Introduce BIG to your personal or professional network
Or organise an event - you can support BIG against breast cancer by volunteering to host a meeting, dinner, or other type of party to raise awareness and funds for BIG.

**Breast Cancer Research Champion**
Make a donation
By making a tax-deductible donation to BIG, you directly support breast cancer research, enabling the discoveries needed to end breast cancer once and for all!
A trial involving 500 patients from about 100 hospitals worldwide

OUR GOAL

The POSITIVE trial will evaluate the pregnancy outcomes and safety of interrupting endocrine therapy for young women with ER+ breast cancer who wish to become pregnant.

More information on: www.BIGagainstbreastcancer.org

(public name: BIG Time for Baby study)