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The idea of publishing an annual report for the institute has been in the air for a very long time. However, we did not like producing every year a cold document highlighting our own results with plain scientific data.

Thus, we came to the conclusion that it would have been better to receive a sincere and frank opinion on our work from external colleagues and collect these commentaries in an editorial product.

Therefore, we consider the IFOM Review a chance for reflection on the progress of knowledge, moving from IFOM activities and results.

A special thanks goes to the authors who generously spent their time and energy to share their views on the progress and perspectives of our research.

Marco Foiani

Francesco Blasi
Prof. Foiani has a Ph.D. in Molecular Biology from the University of Milan (Italy). Since 2002, Prof. Foiani, who is also Head of the Genome Integrity Laboratory at IFOM since its establishment, is Full Professor in Molecular Biology at the University of Milan.

His research interest focuses on the regulatory mechanisms that control genome integrity. Particularly, his work has contributed to elucidate the cellular mechanisms causing genome instability in cancer cells and chromosome abnormalities in certain human syndromes leading to cancer predisposition. Prof. Foiani has more than 80 papers published in international scientific journals.

Since 2008 Prof. Marco Foiani is the Scientific Director of IFOM.

Prof. Foiani was honored with internationally recognized memberships and awards, such as: the European Molecular Biology Organization membership; the Academia Europaea membership; the New York Academy of Sciences membership; the Italian Society of Genetics (AGI) membership; the Italian Society of Biophysics and Molecular Biology (SIBBM) membership; the Award from the Italian Society for Biophysics and Molecular Biology (SIBBM); the Biotec Award promoted by Amgen and Dompé; the “Chiara D’Onofrio” Prize from the Italian Federation of Life Sciences.

He was the founder in 2009 of the European Nanomedicine Foundation (CEN) and vice-president up to 2011.

He is also member of the Scientific Advisory Board of AIRC, the Italian Cancer Research Association, member of the editorial board of Cell and editor and reviewer for top impact factor scientific journals.

Francesco Blasi born in Naples, October 19, 1937.

MD from Naples University Medical School, then two post-Docs at the Max Planck Institut fuer Biophysik (Frankfurt, Germany) and NIH (National Institute of Arthritis and Metabolic Diseases) Bethesda, MD (U.S.A.).

In 1970 back in Italy at the CNR Research Center in the Naples University Medical School, then in 1980 Full Professor at the II Faculty of Medicine of the University of Naples.

Subsequently, Professor at the University of Copenhagen, Denmark and finally in Milano since 1992.

Is at IFOM since 2004, Director of research program Transcriptional Regulation in Development and Cancer.

From 2007 to 2011 coordinates the Molecular Oncology PhD program of SEMM. In 2011 becomes Deputy Director for Science of IFOM.

Has previously been Director of the International Institute of Genetics and Biophysics of CNR in Naples (1980-1983), of the Molecular and Cellular Biology Center in Copenhagen (Denmark), (1988-1992), and of the Department of Cellular Biology and Functional Genomics (1998-2006) at DIBIT, Ospedale San Raffaele.

In 1979 is elected member of EMBO, the prestigious European Molecular Biology Organization, and 1991-1993 of its Council. Since 1992 is a member of Academia Europaea.

Has received national and international prizes and is Author of over 270 research articles in prestigious international Journals, including Nature and Cell.

Has been a member of the Advisory Board of AIRC, Associazione Italiana per la Ricerca sul Cancro, and of the Board of EMBO Journal.

by Klaus Rajewsky

Habent sua fata libelli - that’s what came to my mind when I was asked to comment on the Varano et al. paper. In this case the special fatum is time scale and initial misfortune. The work started fifteen years ago, in 2002, in my laboratory at Harvard Medical School in Boston. A senior postdoc, Stefano Casola, and Simon Raffel, a German MD student, set out to explore whether what we had found for mature B cells in normal physiology also holds true for malignant B cells, namely that cellular survival depends on the expression of the B cell antigen receptor (BCR; Ref. 1). This was an important and therapeutically relevant question, and a clear answer came within a year or so, in the affirmative: In our mouse model of a MYC-driven B cell lymphoma complete cure was achieved when we inducibly deleted the BCR on the surface of the tumor cells in vivo! Fortunately we managed to stop publication of this spectacular result in a (very) high-ranking journal in the last minute: We had fallen into the trap of a technical artifact (2). And thus began the long and windy road towards the resolution of the problem.

Still in Boston, Simon and Stefano showed that, surprisingly, in isolation BCR-negative lymphoma cells proliferated nearly as well as their BCR-positive counterparts; and that BCR-positive cells outcompeted BCR-negative cells in a variety of conditions. At that point Simon had to leave for his home university in Heidelberg, and in 2006 Stefano accepted a PI position at the IFOM in Milano. He built up his lab, hired students, wrote grants and embarked on numerous projects – but never gave up on studying the BCR dependency of B cell lymphomas, about which we continued to discuss. In the meantime the subject became popular and gained practical relevance, because B cell lymphoma therapies targeting the BCR signaling cascade were on the rise. They were not only in line with evidence from mouse models, but also directly supported, indeed suggested, by genetic experiments addressing the “Achilles heel” of human lymphoma cells in vitro (3).

The painstaking experiments carried out in the Casola lab (Varano et al.) on the competition of BCR-positive and -negative MYC-driven lymphoma cells in mice add a new perspective to
the multiple roles that BCR signaling presumably plays in transformed B cells. They suggest scenarios like that of human Burkitt lymphoma, where BCR expression impacts the fitness of the tumor cells in their competition with tumor cells that have lost the BCR. However, while the competitive advantage of the BCR-positive cells is indeed dramatic, variants of BCR-negative cells arise spontaneously and rapidly, often through RAS-mediated MAP kinase activation. The amazing efficiency of this process may be due to the surprising finding that BCR-mediated competitive fitness seems to critically depend on a single signaling pathway, namely PI3K/AKT dependent GSK3β inactivation, promoting MYC activity. Thus, therapeutic strategies targeting the BCR signaling cascade in B cell lymphomas may profit from complementary drugs targeting BCR loss variants. Note in this context that B cells are always in danger of losing BCR expression, given the mechanism of somatic hypermutation operating in these cells on antibody variable region genes to increase antibody affinity during antibody responses.

Beyond these translational considerations, the work of Varano et al. exemplifies the fundamental role of cellular competition in multicellular organisms in general and in our immune system in particular. To which extent and how wild type cells outcompete or actively eliminate spontaneously arising unwanted mutants, and whether such processes mainly apply to cancer pathogenesis or also operate in normal physiology remains a vast area for future research. Indeed, in the case of the B cell system it is striking that the central pathway controlling BCR-dependent lymphoma cell competitive fitness, namely PI3K signaling, has also been shown to control the survival and proliferation of normal B cells at various developmental stages, including that of the mature resting B cell (4).

Acknowledgements: I am grateful to Christine Kocks for critical reading.

References
The B-cell receptor controls fitness of MYC-driven lymphoma cells via GSK3β inhibition

Similar to resting mature B cells, where the B-cell antigen receptor (BCR) controls cellular survival, surface BCR expression is conserved in most mature B-cell lymphomas. The identification of activating BCR mutations and the growth disadvantage upon BCR knockdown of cells of certain lymphoma entities has led to the view that BCR signalling is required for tumour cell survival. Consequently, the BCR signalling machinery has become an established target in the therapy of B-cell malignancies. Here we study the effects of BCR ablation on MYC-driven mouse B-cell lymphomas and compare them with observations in human Burkitt lymphoma. Whereas BCR ablation does not, per se, significantly affect lymphoma growth, BCR-negative (BCR-) tumour cells rapidly disappear in the presence of their BCR-expressing (BCR+) counterparts in vitro and in vivo. This requires neither cellular contact nor factors released by BCR+ tumour cells. Instead, BCR loss induces the rewiring of central carbon metabolism, increasing the sensitivity of receptor-less lymphoma cells to nutrient restriction. The BCR attenuates glycogen synthase kinase 3 beta (GSK3β) activity to support MYC-controlled gene expression. BCR- tumour cells exhibit increased GSK3β activity and are rescued from their competitive growth disadvantage by GSK3β inhibition. BCR- lymphoma variants that restore competitive fitness normalize GSK3β activity after constitutive activation of the MAPK pathway, commonly through Ras mutations. Similarly, in Burkitt lymphoma, activating RAS mutations may propagate immunoglobulin-crippled tumour cells, which usually represent a minority of the tumour bulk. Thus, while BCR expression enhances lymphoma cell fitness, BCR-targeted therapies may profit from combinations with drugs targeting BCR- tumour cells.

[PMID 28562582]
Klaus Rajewsky developed a general method of targeted mutagenesis in mouse embryonic stem cells by introducing bacteriophage- and yeast-derived recombination systems, which opened the way for conditional gene targeting. Using this and other methods in his immunological work, he developed, together with N. A. Mitchison and N. K. Jerne, the antigen-bridge model of T-B cell cooperation, identified germinal centers as the sites of antibody somatic hypermutation, the B cell antigen receptor as a survival determinant of B cells, and the germinal center as a major site of human B cell lymphomagenesis, including Hodgkin lymphoma. Over the last years the work of his group has focused on mechanisms of microRNA control and the development of mouse models of human B cell lymphomas.

After postdoctoral work at the Institut Pasteur in Paris he built an immunology department at the Institute for Genetics at the University of Cologne, where he stayed for 38 years, was the founding Program Coordinator of the EMBL Mouse Biology Program at Monterotondo near Rome, worked for 10 years at Harvard Medical School in Boston, and is since 2012 at the Max-Delbrück-Center for Molecular Medicine in Berlin, Germany.

Klaus Rajewsky won numerous scientific awards and is a member of several learned societies including the National Academy of Sciences of the USA and the American Academy of Arts and Sciences.
For several years biologists have studied the migration of mammalian cells as individual entities placed at the centre of a microscope spotlight. These fundamental investigations led to the establishment of a universally-accepted model for mesenchymal migration valid for all cells adhering to a substrate. Cells advance through repeated cycles of polarized membrane protrusion, new focal adhesion assembly, actomyosin contraction, translocation of the nucleus, and old adhesion disassembly. This model provided a platform to reveal the signalling pathways involved in the regulation of motility and a reference to detect alternative migration schemes such as those appearing in cancer or immune cells. Yet, as much as they tend to be refractory to any stereotyped model, mammalian cells rarely find themselves isolated in the body. In particular, epithelial cells provide a beautiful example of a functional community, that is an ensemble working for a common purpose.

Single epithelial cells behave and migrate according to the mesenchymal scheme. However, as soon as they attain a sufficient density, their dynamics starts to change, migration velocity decreases and coherent, multicellular movements appear. Cells now reach confluency, which literally means ‘flowing together’, a prerequisite for the generation of differentiated, functional epithelia. The phase transition from a gas-like moving group of individual cells to a liquid-like flowing collective is enabled by the establishment of connections between cells, the cell-to-cell junctions, which form supra-cellular mechanical structures. As cell density further increases, collective movements become restricted by the crowding and the monolayer experiences a further transition to a solid-like, jammed phase identifying a quiescent monolayer. This final transition is however reversible, as in various cases epithelial monolayers reanimate collective motility, in order to heal a wound, to execute development, or to descend the path of neoplastic transformation. This entire complexity goes far beyond what we have learnt for single cell motility. To study this exciting phenomena a new access is needed.

The work led by Prof. Scita, to which I had the pleasure to collaborate, introduces a novel approach which exploits synergies from the fields of biology, engineering, and physics, to provide a multiscale comprehension of epithelial unjamming. It all started from the observation that the upregulation of RAB5A, a master regulator of endocytosis, is alone sufficient to reactivate collective motility in quiescent epithelia. At this point the reader should watch the truly amazing...
Altogether this paper introduces several conceptual and methodological innovations, beyond the definition of a novel biological role for RAB5A and endocytosis. From now on we shall consider epithelial monolayers as active materials which are to be studied with a combination of methods from engineering, physics, biology and medicine.

Reference
Aldo Ferrari studied biology at the University and Scuola Normale Superiore of Pisa. He was then selected for a PhD in Physics at the Scuola Normale Superiore in the laboratory of Prof. Fabio Beltram, where he developed mutants of the green fluorescent protein (GFP) for single molecule applications in cell biology and virology. In 2004 he moved to ETH Zurich for a PostDoc in Biochemistry where he applied a combination of physical modelling and live cell fluorescent analysis to investigate lumen formation during epithelial morphogenesis.

In 2007 he went back to Scuola Normale Superiore as research scientist in mechanobiology and material interfaces. During this period he acquired knowledge in material science and engineering fabrication and their application to the study of fundamental biological questions in physiology and development. Since 2009 he is back to ETH Zurich, where he is currently leading a group of Biothermofluidics in the department of Mechanical Engineering. The main activities of the group are in the development of active interfaces supporting the establishment and maintenance of endothelial monolayers, the investigation of interstitial migration of cancer cell using nanofabricated obstacles, and the definition of new protocols for traction force microscopy. In addition, since 2014 he is CTO and head of R&D of the ETH start-up company HYLOMORPH AG commercializing a platform technology to protect body implants from fibrotic encapsulation.

At ETH, Aldo is organizing yearly classes in ‘Mechanobiology’ and ‘Energy Conversion and Transfer in BioSystems’ and serves as editor for Scientific Reports and Frontiers in Biomaterials. He co-organises the international symposium ‘NanoEngineering for Mechanobiology’ which will see its third edition in 2018.
We humans have a difficult time reading through texts with complicated character sequences and frequently stutter. A similar problem is faced by DNA Polymerases when they try to make a copy of DNA. Anyone with a bit of experience in Molecular Biology is well aware of this problem as amplifying repeated sequences by PCR is often problematic and leads to either failure of the reaction or to the presence of errors in the amplified copy. These problems observed in vitro, are nothing else but a recapitulation of the same problem that cells experience every S phase when trying to duplicate repetitive DNA.

While the key to cellular functions lies in genes, only 5-10% of our genome is made of genes or functional elements. The rest, frequently called as “dark-matter”, is to a large extent filled with repetitive sequences including leftovers of viral integrations, transposable elements and alike. Recent estimates indicate that up to two-thirds of the human genome may be present in the human genome. Interestingly, even if repeated sequences comprise most of our genome, they are often neglected in biomedical research studies, in part due to the technical difficulties in working with them. A paradigmatic example are most Next Generation Sequencing datasets, where the analysis starts by excluding repeated sequences since they cannot be mapped to a defined position in the human genome.

While the majority of the repetitive sequences might be non-functional and simply represent scars of past integrations of exogenous DNA, some of them play central roles in cellular biology such as telomeres, centromeres or ribosomal DNA. Consistent with the difficulties that DNA polymerases face during the replication of repetitive sequences, many of them are actually considered “fragile sites”. The instability of ribosomal DNA is well known particularly from yeast studies, and has been even associated to the process of ageing. Telomeres have also recently been found to be fragile, and they contain a unique dedicated pathway to complete their replication. To what extent the replication of other repeats, including centromeres or rDNA, also demands ad-hoc machinery, remains unknown.
To tackle this problem, the group of Vincenzo Costanzo took an original approach that exploited the usefulness of frog oocyte extracts to replicate exogenous DNA. Antoine Aze and colleagues explored how Bacterial Artificial Chromosomes (BACs) containing repeats from human centromeric alpha-satellite sequences were replicated in these extracts, and compared it to the replication of BACs containing a similar GC base content but free of repeats. Their strategy proved to very useful as it yielded important insights into the replication or centromeric DNA.

The first cool observation was that human BACs added to Xenopus extracts form a nucleus, similar to the endogenous one. The BAC containing centromeric repeats (cenBAC) was then replicated, albeit more slowly than the control BAC (cBAC). Subsequent proteomic analysis identified proteins that were enriched (or depleted) from the replicating BACs. These analyses revealed that cenBACs presented a higher presence of DNA repair factors, which might be there as a consequence of DNA breaks arising during DNA replication, or perhaps are already there in a preemptive position “just in case” breaks do happen. Particularly enriched were components of the Mismatch Repair machinery, which would make sense since these factors travel with the replisome to correct mistakes placed by DNA polymerases. It is also possible, however, that the increase in MMR proteins simply reflects a higher amount of replisomes in the cenBACs, which could be due to the more frequent stalling of the replication forks. Other factors enriched in replicating cenBACs were proteins involved in chromosome architecture and topology such as Topoisomerases or components of SMC complexes, likely due to the particular topology of centromeric chromatin.

A surprise, however, was to find that several components from the replication checkpoint were depleted from cenBACs. In vertebrates, the S phase checkpoint is coordinated by the ATR kinase. The activation of ATR is mediated by the ssDNA-binding factor RPA, which together with the recruitment of additional factors such as the allosteric activator TOPBP1, trigger the kinase activity of ATR. In other words, what
the checkpoint first “smells” is actually the accumulation of ssDNA at stalled replication forks. In this context, and as readily imagined by the Costanzo team, one mechanism to explain why checkpoint factors could be depleted from centromeric DNA is that the abundance of ssDNA is somewhat limited at these sequences. And this is exactly what they found.

Using another technique mastered by their team, Electron Microscopy, Aze and colleagues found that replicating cenBACs were full of looped sequences. The most parsimonious interpretation is that when the double helix opens up during DNA replication, the repetitive nature of the sequences will lead to their spontaneous formation of loops and other sort of secondary structures, thus occluding the presence of ssDNA and the activation of the checkpoint. In support of this, the use of Topoisomerase I inhibitors reduced the presence of supercoils and restored checkpoint activation in centromeric DNA.

The story is round and provides one of the first examples and initial insights as to how centromeric DNA is replicated. The discovery that the checkpoint is somewhat silenced at this region is surprising, but makes sense from an evolutionary point of view. ATR activates the alarm when DNA replication problems occur, leading to cellular consequences that can include the activation of apoptosis. Since repetitive sequences will always face problems during their replication, one could envision that the bar to activate the checkpoint should be a bit higher at these regions. In other words, the checkpoint needs to turn a blind eye at repetitive regions.

Finally, as any important study, this work also brings to mind many new questions that could be now tackled. For instance, what about the new and uncharacterized factors that were found in the proteomic studies as enriched in replicating cenBACs? Is it possible that, like in telomeres, the replication of centromeres also uses specialized machinery? Additionally, the group could also exploit this system to address additional questions about centromere replication. I am a good friend of Vincenzo, who I consider one of the most original scientists from our field. I still remember one of our conversations where he told me that he believes that Homologous Recombination factors are not essential in yeast, but yes in mammals, due to the higher presence of repeats in the mammalian genome. I have always liked the idea! They now have the opportunity to address this experimentally. To start with, they could simply explore how the depletion of HR proteins affects the replication of repetitive DNA. Anyway, from what I know of the team, I am sure that I cannot really predict what will be next from their lab. What I do know is that it will help all of us to understand a bit more how life works.
Óscar Fernández-Capetillo (Bilbao, 1974) obtained his PhD from the Universidad del País Vasco working on the role of E2F transcription factors on the development of the immune system with A. Zubiaga. He then joined the laboratory of A. Nussenzweig at the National Cancer Institute, USA, where he started to work on the cellular response to DNA damage (DDR), focusing particularly on the role of the histone variant H2AX and other chromatin-related aspects. After three years at the NCI he joined the CNIO to lead the Genomic Instability Group where his work has continued to focus on chromatin but now mainly concentrates on developing cellular and animal tools for studying the role of the ATR/Chk1 signalling cascade in the protection against cancer and ageing. Since 2016 Oscar is also a Professor of Cancer Therapy at the Karolinska Institute in Sweden.

Replicating repeats: the checkpoint turns a blind eye

The author:

Óscar Fernández-Capetillo
Department of Biological Regulation
A double-strand break can trigger immunoglobulin gene conversion.
Bastianello G, Arakawa H.

A method to convert mRNA into a gRNA library for CRISPR/Cas9 editing of any organism.
Arakawa H.
[PMID: 27574704] IF NA

STAGE-diging: A novel in-gel digestion processing for proteomics samples.
Soffientini P, Bachi A.
[PMID: 27060224] IF 3.867

Tail-anchored Protein Insertion in Mammals: FUNCTION AND RECIPROCAL INTERACTIONS OF THE TWO SUBUNITS OF THE TRC40 RECEPTOR.
[PMID: 27226539] IF 4.258

Identification of Interactions in the NMD Complex Using Proximity-Dependent Biotinylation (BioID).
Schweingruber C, Soffientini P, Ruepp MD, Bachi A, Mühlemann O.
[PMID: 26934103] IF 4.411

24-Hydroxycholesterol participates in pancreatic neuroendocrine tumor development.
[PMID: 27671648] IF 7.06

eEF2K/eEF2 Pathway Controls the Excitation/Inhibition Balance and Susceptibility to Epileptic Seizures.

The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase.
McGarry E, Gaboriau D, Rainey MD, Restuccia U, Bachi A, Santocanale C.
[PMID: 26921344] IF 8.556
DDK dependent regulation of TOP2A at centromeres revealed by a chemical genetics approach.

Minor intron splicing is regulated by FUS and affected by ALS-associated FUS mutants.
[PMID: 27252488] IF 9.643

CDK1 Is a Synthetic Lethal Target for KRAS Mutant Tumours.
[PMID: 26881434] IF 4.411

Blood circulating tumor DNA for non-invasive genotyping of colon cancer patients.
Siravegna G, Bardelli A.
[PMID: 26774880] IF 5.367

Molecular Landscape of Acquired Resistance to Targeted Therapy Combinations in BRAF-Mutant Colorectal Cancer.
[PMID: 27312529] IF 8.556

Acquired RAS or EGFR mutations and duration of response to EGFR blockade in colorectal cancer.
Nat Commun. 2016 Dec 8;7:13665. doi: 10.1038/ncomms13665.
[PMID: 27929064] IF 11.329

MM-151 overcomes acquired resistance to cetuximab and panitumumab in colorectal cancers harboring EGFR extracellular domain mutations.
[PMID: 26843189] IF 16.264
Polyclonal Secondary FGFR2 Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma.
[PMID: 28034880] IF 19.783

MET-Driven Resistance to Dual EGFR and BRAF Blockade May Be Overcome by Switching from EGFR to MET Inhibition in BRAF-Mutated Colorectal Cancer.
[PMID: 27325282] IF 19.783

A Vulnerability of a Subset of Colon Cancers with Potential Clinical Utility.
[PMID: 27058664] IF 28.71

The transcription factor Prep1 controls hepatic insulin sensitivity and gluconeogenesis by targeting nuclear localization of FOXO1.
Kulebyakin K, Penkov D, Blasi F, Akopyan Z, Tkachuk V.
[PMID: 27815072] IF 2.371

The flexibility of a homeodomain transcription factor heterodimer and its allosteric regulation by DNA binding.
Mathiasen L, Valentini E, Boivin S, Cattaneo A, Blasi F, Svergun DI, Bruckmann C.
[PMID: 27390177] IF 4.237

Identification of Substrates of Protein-Group SUMOylation.
Psakhye I, Jentsch S.
[PMID: 27631809] IF 0.79

Priming for tolerance and cohesion at replication forks.
Branzei D, Szakal B.
[PMID: 26889705] IF 3.13

DNA damage tolerance by recombination: Molecular pathways and DNA structures.
Branzei D, Szakal B.
[PMID: 27236213] IF 3.929
Chromatin determinants of the inner-centromere rely on replication factors with functions that impart cohesion.
Abe T, Kawasumi R, Arakawa H, Hori T, Shirahige K, Losada A, Fukagawa T, Branzei D.
[PMID: 27636994] IF 5.008

Smc5/6 Mediated Sumoylation of the Sgs1-Top3-Rmi1 Complex Promotes Removal of Recombination Intermediates.
[PMID: 27373152] IF 7.87

DNA damage tolerance.
Branzei D, Psakhye I.
[PMID: 27060551] IF 8.851

Esc2 promotes Mus81 complex-activity via its SUMO-like and DNA binding domains.
Sebesta M, Urulangodi M, Stefanowie B, Szakal B, Pacesa M, Lisby M, Branzei D, Krejci L.

DNA damage tolerance branches out toward sister chromatid cohesion.
Branzei D.
[PMID: 27308553] IF NA

Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study.
[PMID: 27062684] IF 2.591

p53 Maintains Genomic Stability by Preventing Interference between Transcription and Replication.
Yeo CQ, Alexander I, Lin Z, Lim S, Aning OA, Kumar R, Sangthongpitag K, Pendharkar V, Ho VH, Cheok CF.
[PMID: 27052176] IF 7.87

Tumor-derived circulating endothelial cell clusters in colorectal cancer.
[PMID: 27358499] IF 16.264
Studying essential DNA metabolism proteins in Xenopus egg extract.
Sannino V, Kolinjivadi AM, Baldi G, Costanzo V.
[PMID: 27759152] IF 1.753

Replication, checkpoint suppression and structure of centromeric DNA.
Romeo F, Falbo L, Costanzo V.
[PMID: 27893298] IF 3.13

GEMC1 is a critical regulator of multiciliated cell differentiation.
[PMID: 26933123] IF 9.643

Structure of human Cdc45 and implications for CMG helicase function.
Simon AC, Sannino V, Costanzo V, Pellegrini L.
[PMID: 27189187] IF 11.329

Centromeric DNA replication reconstitution reveals DNA loops and ATR checkpoint suppression.
Aze A, Sannino V, Soffientini P, Bachi A, Costanzo V.
[PMID: 27111843] IF 18.699

Partial loss of VE-cadherin improves long-term outcome and cerebral blood flow after transient brain ischemia in mice.
Gertz K, Kronenberg G, Uhlemann R, Prinz V, Marquina R, Corada M, Dejana E, Endres M.
[PMID: 27538712] IF 1.961

Tie2 Expressing Monocytes in the Spleen of Patients with Primary Myelofibrosis.
[PMID: 27281335] IF 4.411

Angiomotin like-1 is a novel component of the N-cadherin complex affecting endothelial/pericyte interaction in normal and tumor angiogenesis.
[PMID: 27464479] IF 5.228
Endothelial Cells Lining Sporadic Cerebral Cavernous Malformation Cavernomas Undergo Endothelial-to-Mesenchymal Transition.
[PMID: 26839352] IF 5.787

β-Catenin Is Required for Endothelial Cyp1b1 Regulation Influencing Metabolic Barrier Function.
Ziegler N, Awwad K, Fisslthaler B, Reis M, Devraj K, Corada M, Minardi SP, Dejana E, Plate KH, Fleming I, Liebner S.
[PMID: 27559173] IF 5.924

The endothelial adaptor molecule TSAd is required for VEGF-induced angiogenic sprouting through junctional c-Src activation.
[PMID: 27436360] IF 7.359

Endothelial cells are progenitors of cardiac pericytes and vascular smooth muscle cells.
[PMID: 27516371] IF 11.329

Glycolytic regulation of cell rearrangement in angiogenesis.
[PMID: 27436424] IF 11.329

VEGFR2 pY949 signalling regulates adherens junction integrity and metastatic spread.
[PMID: 27005951] IF 11.329

Telomere-Internal Double-Strand Breaks Are Repaired by Homologous Recombination and PARP1/Lig3-Dependent End-Joining.
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[PMID: 27806302] IF 7.87

A Simple and Resource-efficient Setup for the Computer-aided Drug Design Laboratory.
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[PMID: 27647771] IF 1.57
Software Infrastructure for Computer-aided Drug Discovery and Development, a Practical Example with Guidelines.
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[PMID: 27546042] IF 1.57

Thaler F, Mercurio C.
[PMID: 27730846] IF 4.626

Transcription and DNA Damage: Holding Hands or Crossing Swords?
D'Alessandro G, d'Adda di Fagagna F.
[PMID: 27825959] IF 4.517

DICER, DROSHA and DNA damage response RNAs are necessary for the secondary recruitment of DNA damage response factors.
Francia S, Cabrini M, Matti V, Oldani A, d'Adda di Fagagna F.
[PMID: 26906421] IF 4.706

NOTCH1 Inhibits Activation of ATM by Impairing the Formation of an ATM-FOXO3a-KAT5/Tip60 Complex.
Adamowicz M, Vermezovic J, d'Adda di Fagagna F.
[PMID: 27524627] IF 7.87

Patients with genetically heterogeneous synchronous colorectal cancer carry rare damaging germline mutations in immune-related genes.
[PMID: 27377421] IF 11.329

Advances in the characterization of RNA-binding proteins.
Marchese D, de Groot NS, Lorenzo Gotor N, Livi CM, Tartaglia GG.
[PMID: 27503141] IF 4.519

The prognostic potential of alternative transcript isoforms across human tumors.
Trincado JL, Sebestyén E, Pagés A, Eyras E.
[PMID: 27535130] IF 5.7
Metformin with everolimus and octreotide in pancreatic neuroendocrine tumor patients with diabetes.

ATR-mediated regulation of nuclear and cellular plasticity.
Kidiyoor GR, Kumar A, Foiani M.

Nucleolytic processing of aberrant replication intermediates by an Exo1-Dna2-Sae2 axis counteracts fork collapse-driven chromosome instability.

Genome-wide localization of Rrm3 and Pif1 DNA helicases at stalled active and inactive DNA replication forks of Saccharomyces cerevisiae.
Rossi SE, Carotenuto W, Giannattasio M.

Primary Cerebellar Neuroendocrine Tumors: Chimeras or Real Entities? A Case Report with a 6-Year Follow-Up.

miR-342 overexpression results in a synthetic lethal phenotype in BRCA1-mutant HCC1937 breast cancer cells.
Crippa E, Folini M, Pennati M, Zaffaroni N, Pierotti MA, Gariboldi M.

Mechanical confinement triggers glioma linear migration dependent on formin FHOD3.
How cells respond to environmental cues - insights from bio-functionalized substrates.
[PMID: 27856508] IF 4.706

NuMA Phosphorylation by Aurora-A Orchestrates Spindle Orientation.
Gallini S, Carminati M, De Mattia F, Pirovano L, Martini E, Oldani A, Asteriti IA, Guarguaglini G, Mapelli M.
[PMID: 26832443] IF 8.983

Stochastic timing in gene expression for simple regulatory strategies.
Co AD, Lagomarsino MC, Caselle M, Osella M.

Growth factors, aging and age-related diseases.
Balasubramanian P, Longo VD.
[PMID: 26883276] IF 1.448

Fasting and Caloric Restriction in Cancer Prevention and Treatment.
Brandhorst S, Longo VD.
[PMID: 27557543] IF 2.65

A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms.
[PMID: 27239035] IF 7.87

Dietary Interventions, Cardiovascular Aging, and Disease: Animal Models and Human Studies.
Mirzaei H, Di Biase S, Longo VD.
[PMID: 27174953] IF 11.551

Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan.
Longo VD, Panda S.
[PMID: 27304506] IF 17.303
Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions.
Vernieri C, Casola S, Foiani M, Pietrantonio F, de Braud F, Longo V.
[PMID: 27872127] IF 19.783

Enhancing Stem Cell Transplantation with “Nutri-technology”.
Longo VD, Cortellino S.
[PMID: 27912088] IF 22.387

Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity.
[PMID: 27411588] IF 23.523

Dietary restriction with and without caloric restriction for healthy aging.
Lee C, Longo V.
[PMID: 26918181] IF NA

Di Biase S, Longo VD.
[PMID: 27314084] IF NA

Different Golgi ultrastructure across species and tissues: Implications under functional and pathological conditions, and an attempt at classification.
Mironov AA, Sesorova IS, Seliverstova EV, Beznoussenko GV.
[PMID: 28007425] IF 1.258

Three-dimensional and immune electron microscopic analysis of the secretory pathway in Saccharomyces cerevisiae.
[PMID: 27590193] IF 2.78

Resetting cancer stem cell regulatory nodes upon MYC inhibition.
[PMID: 27852622] IF 7.739
Association of genetic susceptibility variants for type 2 diabetes with breast cancer risk in women of European ancestry.
[PMID: 27053251] IF 2.68

Haplotype analyses of the c.1027C>T and c.2167>2168delAT recurrent truncating mutations in the breast cancer-predisposing gene PALB2.
[PMID: 27624329] IF 4.085

Association of breast cancer risk in BRCA1 and BRCA2 mutation carriers with genetic variants showing differential allelic expression: identification of a modifier of breast cancer risk at locus 11q22.3.
[PMID: 27796716] IF 4.085

Fine-Scale Mapping at 9p22.2 Identifies Candidate Causal Variants That Modify Ovarian Cancer Risk in BRCA1 and BRCA2 Mutation Carriers.
[PMID: 27463617] IF 4.411

RAD51B in Familial Breast Cancer.
[PMID: 27149063] IF 4.411

Genetic predisposition to ductal carcinoma in situ of the breast.
[PMID: 26884359] IF 5.211
Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the Consortium of Investigators of Modifiers of BRCA1/2.
[PMID: 26857456] IF 5.211

Identification of independent association signals and putative functional variants for breast cancer risk through fine-scale mapping of the 12p11 locus.
[PMID: 27459855] IF 5.211

Fine scale mapping of the 17q22 breast cancer locus using dense SNPs, genotyped within the Collaborative Oncological Gene-Environment Study (COGS).
[PMID: 27600471] IF 5.228

Fine-scale mapping of 8q24 locus identifies multiple independent risk variants for breast cancer.
[PMID: 27087578] IF 5.531

PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS.
[PMID: 27595995] IF 5.65

No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing.
[PMID: 26921362] IF 5.65
Whole-exome sequencing and targeted gene sequencing provide insights into the role of PALB2 as a male breast cancer susceptibility gene.
[PMID: 27648926] IF 8.556

Identification of four novel susceptibility loci for oestrogen receptor negative breast cancer.
[PMID: 27117709] IF 11.329

Functional mechanisms underlying pleiotropic risk alleles at the 19p13.1 breast-ovarian cancer susceptibility locus.
Nat Commun. 2016 Sep 7;7:12675. doi: 10.1038/ncomms12675.
[PMID: 27601076] IF 11.329

Genetically Predicted Body Mass Index and Breast Cancer Risk: Mendelian Randomization Analyses of Data from 145,000 Women of European Descent.
[PMID: 27551723] IF 13.585

Genome-Wide Meta-Analyses of Breast, Ovarian, and Prostate Cancer Association Studies Identify Multiple New Susceptibility Loci Shared by at Least Two Cancer Types.
[PMID: 27432226] IF 19.783
Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170.
[PMID: 26928228] IF 31.616

Strategies to Detect Endogenous Ubiquitination of a Target Mammalian Protein.
Sigismund S, Polo S.
[PMID: 27613032] IF 0.79

In Vitro Ubiquitination: Self-Ubiquitination, Chain Formation, and Substrate Ubiquitination Assays.
Maspero E, Polo S.
[PMID: 27613033] IF 0.79

Myosin VI Contains a Compact Structural Motif that Binds to Ubiquitin Chains.
[PMID: 26971995] IF 7.87

USP9X Controls EGFR Fate by Deubiquitinating the Endocytic Adaptor Eps15.
Savio MG, Wollscheid N, Cavallaro E, Algisi V, Di Fiore PP, Sigismund S, Maspero E, Polo S.
[PMID: 26748853] IF 8.983

HUWE1 is a critical colonic tumour suppressor gene that prevents MYC signalling, DNA damage accumulation and tumour initiation.
[PMID: 28003334] IF 9.547

Diverse functions of myosin VI elucidated by an isoform-specific α-helix domain.
[PMID: 26950368] IF 13.338

Chapter Six - The Ubiquitin Network in the Control of EGFR Endocytosis and Signaling.
Conte A, Sigismund S.
[PMID: 27378759] IF 3.488
Endocytic control of signaling at the plasma membrane.
Barbieri E, Di Fiore PP, Sigismund S.
[PMID: 26872272] IF 8.851

Sensitive and affordable diagnostic assay for the quantitative detection of anaplastic lymphoma kinase (ALK) alterations in patients with non-small cell lung cancer.
[PMID: 27206799] IF 5.008

Optimization and Standardization of Circulating MicroRNA Detection for Clinical Application: The miR-Test Case.
[PMID: 27127244] IF 7.457

Modelling TFE renal cell carcinoma in mice reveals a critical role of WNT signaling.
[PMID: 27668431] IF 8.303

An Aggressive Subtype of Stage I Lung Adenocarcinoma with Molecular and Prognostic Characteristics Typical of Advanced Lung Cancers.
[PMID: 27358486] IF 8.738

The pseudophosphatase STYX targets the F-box of FBXW7 and inhibits SCFFBXW7 function.
[PMID: 28007894] IF 9.643

The EGFR-specific antibody cetuximab combined with chemotherapy triggers immunogenic cell death.
[PMID: 27135741] IF 30.357

Nucleophosmin leukemogenic mutant activates Wnt signaling during zebrafish development.
[PMID: 27486814] IF 5.008
Direct interaction between exocyst and Wave complexes promotes cell protrusions and motility.

Differential identity of Filopodia and Tunneling Nanotubes revealed by the opposite functions of actin regulatory complexes.
Delage E, Cervantes DC, Pénard E, Schmitt C, Syan S, Disanza A, Scita G, Zurzolo C.

RAB2A controls MT1-MMP endocytic and E-cadherin polarized Golgi trafficking to promote invasive breast cancer programs.

Increasing the public health potential of basic research and the scientist satisfaction. An international survey of bioscientists.
Scita G, Sorrentino C, Boggio A, Hemenway D, Ballabeni A.

Geometric control and modeling of genome reprogramming.
Uhler C, Shivashankar GV.

Nuclear transport of paxillin depends on focal adhesion dynamics and FAT domains.
Sathe AR, Shivashankar GV, Sheetz MP.

Matrix mechanics controls FHL2 movement to the nucleus to activate p21 expression.
Nakazawa N, Sathe AR, Shivashankar GV, Sheetz MP.
Proc Natl Acad Sci U S A. 2016 Nov 1;113(44):E6813-E6822. [PMID: 27742790] IF 7.06

Urokinase links plasminogen activation and cell adhesion by cleavage of the RGD motif in vitronectin.
De Lorenzi V, Sarra Ferraris GM, Madsen JB, Lupia M, Andreasen PA, Sidenius N.
Novel Antitransferrin Receptor Antibodies Improve the Blood-Brain Barrier Crossing Efficacy of Immunoliposomes.
Gregori M, Orlando A, Re F, Sesana S, Nardo L, Salerno D, Mantegazza F, Salvati E, Zito A, Malavasi F, Masserini M, Cazzaniga E.
[PMID: 26852859] IF 2.641

When membranes need an ESCRT: endosomal sorting and membrane remodelling in health and disease.
Alfred V, Vaccari T.
[PMID: 27631343] IF 1.823

Control of lysosomal biogenesis and Notch-dependent tissue patterning by components of the TFEB-V-ATPase axis in Drosophila melanogaster.
[PMID: 26727288] IF 9.108

An essential step of kinetochore formation controlled by the SNARE protein Snap29.
Morelli E, Mastrodonato V, Beznoussenko GV, Mironov AA, Tognon E, Vaccari T.
[PMID: 27647876] IF 9.643

Dynamic phosphorylation of Histone Deacetylase 1 by Aurora kinases during mitosis regulates zebrafish embryos development.
[PMID: 27458029] IF 5.228
Corporate profile

IFOM, the FIRC Institute of Molecular Oncology, is an Italian highly technology, non-profit research centre supported by FIRC, the Italian Foundation for Cancer Research. Research conducted at IFOM aims to understand the molecular processes responsible for the onset and development of cancer.

To meet the demands of modern-day science, IFOM created a research environment where scientists from the major national scientific institutions in the Milan area could collaborate and pool their organisational, economical and cultural resources. The creation of a research institute “network” was the first of its kind in Italy and has made IFOM an internationally competitive research centre in molecular oncology and functional genomics.

IFOM has been recognised as a Centre of Excellence for Research by the Lombardy Regional Council, which also contributed to IFOM’s development.

Having established a solid base in basic research, IFOM is now concentrating its efforts on translational research for the rapid transfer of scientific findings from the laboratory to diagnostic and therapeutic clinical practice. IFOM has adopted a strong international approach, fostering partnerships with world-class research institutes in Singapore and India. Thanks to these agreements, IFOM is becoming an important player in the global landscape of cancer research institutions.

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