
CRG
Centre
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Regulation
Executive
Summary
2015
Understanding the
complexity of life
2015
A year in review
EXCELENCIA
SEVERO
OCHOA

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Foreword

The year 2015 has been a pivotal one for the future of the CRG. First, as of July 1, 2015, the National Centre for Genomic Analysis (Centro Nacional de Análisis Genómico, CNAG) was incorporated into the CRG, to create the CNAG-CRG. The incorporation of the CNAG has helped position the CRG as an institute of reference for genome analysis in Europe. Second, in late 2014 the EMBL Council of Member States decided to establish a new outstation in Barcelona with a focus on Tissue Biology and Disease Modeling. Significant groundwork was accomplished over the course of 2015. These changes and 'works-in-progress', in addition to the fact that over the next few years many young PIs will be leaving the institute, have prompted us to start preparing a 2017-2022 Strategic Plan to define our research strategy and key priorities. The Plan will be finished in 2016.

In April 2015, the Cell and Developmental Biology programme was evaluated by our Scientific Advisory Board, which generally praised the quality of the science developed over the previous four years. We also saw the departures of two key figures: Johannes Jaeger, who left to become Director of the Konrad Lorenz Institute (KLI) in Klosterneuburg, Austria, and Heinz Himmelbauer, Head of the Genomics Unit, to become a PI at the University of Natural Resources and Life Sciences in Vienna, also in Austria.

In the realm of funding, James Sharpe, Juan Valcárcel and myself were awarded an ERC Advanced Grant in 2015, and secured several coordinated European projects under the H2020 funding scheme, continuing with our excellent track record in this field. Along the same lines, it is worth highlighting the launch of the coordinated EU project, LIBRA, whose main purpose is the promotion of women in science, involving all EU-LIFE institutes. The CRG has taken a serious approach to gender balance and equal opportunities and as a consequence is developing new initiatives like the mentoring programme for postdoctoral researchers and PhD students, specific grants for female scientists, inspirational seminars, etc. Promoting women's advancement in science is also one of the main foci of the new Strategic Plan.

In terms of public engagement, we are proud of the citizen science project "Saca la Lengua" ("Stick Out Your Tongue"). This project, the first citizen science initiative led by the CRG, was co-financed by "la Caixa" Bank Foundation and the Severo Ochoa institutional grant. It has been running throughout the year, following a tight schedule of samples collection (nearly 2,000 in 41 schools around Spain), talks, bioinformatics courses for teachers, bioinformatics challenges and the final contest, etc. This frantic activity led to 196 articles in the press and on-line media, as well as radio and TV coverage.

We should also mention the distinguished awards that have recognized the scientific commitment and merit of several senior scientists: our former director, Miguel Beato received the 2015 Preclinical Biomedical Research Lilly Foundation Award; Isabelle Vernos was awarded the 'Narcís Monturiol Medal' recognizing her contribution to the development of science and technology in Catalonia; and Pia Cosma received the 2015 'City of Barcelona Award' for her recent work offering a new vision on how DNA is organised and packaged.

Last, it is important to note that the CRG launched the Alumni Engagement Programme in 2015. It seeks to establish a lifelong relationship with our alumni and staff by creating a strong CRG Global Community. We now have more than 1,000 alumni all over the world and our goal is to create a vibrant and exciting community by promoting interaction among alumni and staff, highlighting their achievements and sparking our alumni's success, providing them with rewarding opportunities to serve the CRG, its faculty and students, and promoting science internationally.

We firmly believe that the CRG is now consolidated as a top international biomedical research institute, but we will continue to strive for scientific excellence, endeavouring to contribute towards the health and economic prosperity of our society.

Luis Serrano
Director

Scientific Highlights

Spotting the molecular fingerprint of multiple sclerosis

Going to hospital with neurological problems is worrying enough. But what if it's an early sign of a more serious illness?

A debilitating long-term disease, multiple sclerosis (MS for short) affects nerves in the brain and spinal cord, causing small patches of hard tissue to form. Nobody knows exactly what causes it and there is no cure, although the sooner someone is diagnosed with MS, the sooner they can be monitored and offered treatments that can slow down its progression.

Every year, many thousands of people go to the doctor with symptoms that might be the early signs of MS, including tiredness, foggy thinking, stumbling while walking numbness or pins and needles in the skin, or problems with their eyesight.

If it's the first time they have ever experienced problems like this, it's known as Clinically Isolated Syndrome (CIS). However, this may just be a one-off occurrence, and the symptoms seen in CIS can also be the hallmarks of other conditions.

So how can doctors tell if someone coming into their clinic with CIS is likely to go on to get MS, and will benefit from early treatment for the disease?

That's the question that Eva Borràs and Eduard Sabidó, from the Proteomics Unit at the CRG and Universitat Pompeu Fabra, set out to answer, with the help of doctors working with MS patients at the University Hospital in Vall d'Hebron, also in Barcelona.

FINDING THE FINGERPRINT

Borràs, Sabidó and their colleagues were lucky enough to have access to a valuable and vital resource: samples of cerebrospinal fluid (liquid from the brain and spinal cord) from patients who had come into the hospital with CIS, as well as clinical data tracking whether they went on to develop MS months or even years later.

"Taking cerebrospinal fluid is a routine test for people who come into the hospital with a first episode of neurologic symptoms," explains Borràs. "The samples were there, as was the clinical information about these patients – we just had to apply our knowledge and technology to find a molecular fingerprint that could help clinicians predict the patient's outcome."

To pin down this fingerprint, Borràs and Sabidó used a technique called mass spectrometry, which enables scientists to identify all the different protein molecules in a sample by smashing them into pieces and weighing them. After careful analysis, they spotted a few key differences in the fluid samples from people who went on to develop MS, compared to those who didn't.

Narrowing it down even further, the researchers discovered that measuring the amounts of just two protein molecules – known as CH3L1 and CNDP1 – in cerebrospinal fluid was enough to predict the chances of someone with CIS developing MS in the future.

TESTING TIMES

Discovering that the levels of just two molecules can reveal whether someone is going to develop MS is a hugely important breakthrough. The big question is: what happens next?

The mass spectrometry technique that Borràs and Sabidó use in their lab isn't widely available in hospitals, so an alternative test will need to be developed for more widespread clinical use. As Sabidó explains, "We might be able to create a test called an ELISA, where these two proteins are detected with antibodies. This kind of test is standard in hospitals everywhere. We have filed a patent and are talking to commercial partners who might be interested in helping us develop it."

But that's not all.

"We have a parallel research project with the same collaborators in the hospital which is not prediction of the disease, but understanding the mechanisms that lie underneath," he says. "We are now analysing a lot of additional samples to try and find the key molecules that are driving MS."

The results of this study have recently been published in the journal Molecular and Cellular Proteomics. Although translating these exciting findings from the lab into a test that doctors can use can take some time, this is certainly an important step forward for worried patients and their families. And by finding the molecular culprits that lie at the heart of the disease, Sabidó hopes that his team's work might one day lead to new treatments for MS patients too.

ORIGINAL PAPER

Borràs E, Cantó E, Choi M, Maria Villar L, Álvarez-Cermeño JC, Chiva C, Montalban X, Vitek O, Comabella M, Sabidó E. 'Protein-Based Classifier to Predict Conversion from Clinically Isolated Syndrome to Multiple Sclerosis.' *Mol Cell Proteomics*, 15(1):318-28 (2015).

Zipping up

Imagine you're going on holiday and your suitcase is packed full. So full, in fact, that it won't close. You could apply more force, kneeling on the case and tugging harder on the zipper until it shuts. But what if the things in the suitcase actually got smaller?

Unfortunately for tourists, there is no magical process that makes your clothes shrink to fit in your bag. Yet, according to research from Jérôme Solon and his team in the Biomechanics of Morphogenesis lab at the CRG, this is exactly what happens during an equivalent biological process known as dorsal closure, which happens during the development of a fruit fly embryo.

Shaped like a rugby ball and less than a millimetre long, the developing fly embryo undergoes many changes as it tucks and folds into the correct structure. During dorsal closure, two sheets of cells at the surface of the embryo come together, closing up from each end across the gap just like the zippers of a suitcase being pulled shut, sealing the innards of the embryo inside. But exactly how it works is a mystery.

FEEL THE FORCE

Scientists now know that this biological 'zipper' is driven by tiny molecular cables and motors inside cells, known as actin and myosin. In the same way that you can close an overly-full suitcase by tugging harder on the zip and squeezing on the case, it was believed that the increased force needed to 'zip up' an embryo during dorsal closure was generated by actin and myosin in the cells surrounding the gap, as well as in the cells inside it (known as the amnioserosa).

But when Solon and his team started investigating the actin and myosin-generated forces in the cells at the surface of the embryo, they found that they didn't change at all. This was strange. In order to squeeze the sheets of cells shut, there needs to be some kind of increasing force pushing from the outside or pulling from inside (or both), otherwise nothing will change and the gap won't close.

Imagine maintaining a constant amount of pressure on the outside of an over-packed suitcase and its zipper – without increasing the pressure of your pushing and tugging, you're never going to get it shut. But where was this force coming from?

Solon and his team found that this force originates from two mechanisms working together. Part of it comes from a molecular 'purse string' – a long cable of actin and myosin threading through the cells surrounding the gap on the embryo's surface. Like tugging harder on the zipper of a suitcase, this thread tightens up as the gap closes, pulling the sheets of cells together. But that's not enough to zip up the developing embryo.

The breakthrough came when Solon and his team worked out a completely new way of monitoring the cells in the developing embryo in three-dimensional space, as well as over time.

"People so far have only looked at what is happening on the surface of the embryo," explains Solon. "This is the first time that we looked at the entire volume of the tissue, to really understand the mechanics."

By doing this, they discovered the explanation for how dorsal closure was happening. It wasn't that the cells were generating more forces by adding more motors to pull the tissue closed sheets: the change was simply being driven by the cells inside the gap (the amnioserosa) getting smaller.

CASE CLOSED

This shrinkage is a hallmark of a particular type of cell death called apoptosis. Exactly on cue, all the cells in the amnioserosa start dying in a kind of biological mass-suicide, losing water and shrivelling up. And it's this change in size, combined with the purse string around the gap, that generates the forces needed to zip up the embryo.

"It was very surprising to find that the cells inside are losing volume," Solon says, "and we took a lot of measurements to convince ourselves that this was happening. Nobody had really thought that apoptosis could generate force in this way."

To return to the over-packed suitcase, this would be like a holidaymaker's belongings shrinking within the case, pulling it shut from the inside.

While this is all very useful for zipping up fruit fly embryos, Solon's work – published in the journal Developmental Cell – potentially has a much wider impact. "The more general idea behind this story is about how two sheets of cells seal shut, which also happens during wound healing," he says. "We know that the genes and processes involved in this are highly conserved across the animal kingdom so it's likely the same system is at work."

HEALING TOUCH

Although he has only done experiments using fruit fly embryos, when Solon went back to look at old research papers he found some tantalising suggestions that wounds in the skin may be sealing shut in the same way.

"I found some publications from about 15 years ago on wound healing in mice. People had found that fibroblast cells which are initially covering the wound will activate apoptosis before it closes up. So we could perfectly imagine that similar mechanisms to the ones we have found in flies would take place here."

There are other situations in development where this process could be at work too. As Solon explains, "One example is in the developing brain of vertebrates. There are waves of apoptosis and these shrinking cells could be responsible for sculpting the brain, but this is not entirely clear."

By coupling cell death directly to force generation in this way, organisms avoid the potential problems of failing to get the timing right between closing biological seams and getting rid of unwanted cells in the gap. If cells die too soon, before the edges have sealed, then there will be a hole. But if the 'zip' shuts over living tissue, there could be unwanted lumps and bumps.

What's more, there are still some mysteries that Solon wants to solve. "We still don't know how apoptosis is activated in all the cells simultaneously, which is something I find amazing. They all decide in a few tens of minutes to die, and they all take that decision together. We are also developing mathematical models to figure out exactly how the forces work."

While most of us might be packing our suitcases for a summer holiday and wondering how to make it all fit, Solon and his team are busy trying to understand how nature has managed to solve this problem already.

ORIGINAL PAPER

Saias L, Swoger J, D'Angelo A, Hayes P, Colombelli J, Sharpe J, Salbreux G, Solon J.
'Decrease in Cell Volume Generates Contractile Forces Driving Dorsal Closure.'
Dev Cell, 33(5):611-21 (2015).

Have a heart

Building a complex machine is a tricky job, taking expert skill and teamwork. And by studying the molecular 'workers' in our cells, researchers are starting to understand how a complex biological machine – the heart – is built as a fetus develops in the womb.

The 'workers' in this story are molecules called Polycomb proteins. They're found in many types of plants and animals, playing important roles in turning genes off when they're no longer needed. If they don't function properly it causes big problems in development, as important genes controlling the development of all kinds of organs and structures don't know when to shut down.

Fruit flies have just four Polycomb proteins, which work together in a group (known as a Polycomb complex) to get all their various jobs done. But mammals have many more. For each of the four components of the Polycomb complex, there are between two and six distinct versions, giving around 200 different possible combinations. So what do they all do?

It's a question that fascinates Luciano Di Croce, who leads the Epigenetic Events in Cancer group at the CRG focusing on how mistakes in turning genes on and off can lead to cancer and other problems.

BEATING IN A PETRI DISH

To figure out the functions of all these possible Polycomb combinations during mammalian development, Di Croce and his team turned to mouse embryonic stem (ES) cells. These are immortal cells originally collected from a mouse embryo when it is just a tiny football of cells, just a few days old. What's really special about them is that they can be persuaded to become any cell type on the body (a process known as differentiation), just by adding the right chemical factors and treating them in certain ways.

"We can take the cells that have been growing for a long time in a Petri dish, which means that we don't need to use animals," Di Croce explains. "We take the cells and differentiate them into all kinds of cell types – nerve cells, other types of brain cells, heart muscle cells and so on. Then we see what happens when we get rid of one of these Polycomb proteins, or another family member, or different combinations."

In some cases, removing one of the Polycomb proteins makes no difference to the ability of the ES cells to differentiate into any type of cell. But Di Croce noticed a crucial Polycomb component, called Mel18, that seemed to be essential for turning the cells into cardiomyocytes – the muscle cells in the heart.

"We can look down the microscope and see these heart muscle cells beating in the dish – it is quite amazing! But when we remove Mel18, they don't become muscle and they don't beat."

Being able to turn stem cells into cardiomyocytes in the lab is a major technical step forward. And clearly, based on these experiments – published in the journal Cell Stem Cell – Mel18 is playing a vital role in heart development. But Polycomb proteins work in four-part complexes, so Di Croce also wanted to find its molecular 'colleagues' too.

BRINGING IN THE EXPERTS

When the heart develops inside a fetal mouse or human, it doesn't just pop into existence, fully formed. The cells that will eventually form the heart have to go through various stages, each involving a range of genes being switched on and off, to prepare them for the next stage in the process.

First, the cells decide they are going to become a type of tissue called mesoderm - literally the 'middle layer' of the embryo, which is the precursor to tissues such as muscle, cartilage and bone – and lose their ability to generate any other types of cells. Then a subset of these mesoderm cells make the commitment to becoming cardiomyocytes, switching on muscle genes and organising themselves into a beating heart.

Through careful analysis, Di Croce and his team discovered that Mel18 was involved in controlling gene activity along every step of this pathway. But he found that other Polycomb proteins join or leave the complex at various stages, leading to three different combinations along the way.

To use an analogy with the skilled craftspeople we met at the beginning of this story, Mel18 is the 'expert' in heart building. It's needed during every step of the process from ES cell to cardiomyocyte. But the other components switch in and out during different stages, only bringing their skills when they're needed.

There's an interesting twist to the story too. Until now, researchers have only ever found that Polycomb complexes can switch off genes. But Di Croce and his team discovered that they can also switch genes on too.

"This was completely new in the field," he says. "All these years it's been considered to be a repressor of gene activity, but we found that it could help turn genes on. It was very unexpected, and we crossed our fingers that we were not wrong. But we did the experiment so many times to make sure it wasn't an artefact, and when we got the same result we thought maybe this is what the cells are telling us, and it is our duty to publish the data so people can judge it. And now other labs are finding that Polycomb has an activating function, so I think we were right."

FUTURE HOPES

It's always nice to be right, but understanding how Mel18 and its molecular colleagues work to build heart muscle cells also has important implications for human health.

As part of their study, Di Croce and his team investigated which genes are affected when Mel18 is removed. Intriguingly, all the genes they found are involved in human diseases affecting the heart muscle, suggesting there is a clear link between human heart disease, Mel 18 and its Polycomb partners.

There are also implications for so-called regenerative medicine, growing human cells, tissue and even organs from stem cells in the lab for transplanting into patients. Knowing exactly what's going on as stem cells change into cardiomyocytes is vital for making sure future lab-grown hearts are built properly at a molecular level.

And there's a third angle, as Di Croce explains, based on the techniques that he and his team have developed to grow heart muscle cells in the lab. "Say you want to test whether a drug has toxic side effects on someone's heart, or test different drugs to find the best one. You could just inject drugs into the patient every single day. But we can now take cells from the patient and turn them into cardiomyocytes, which can be tested to see which compounds work."

Watching these wriggling cells beating in their plastic dishes, it's easy to see how this kind of approach could one day become a hearty success.

ORIGINAL PAPER

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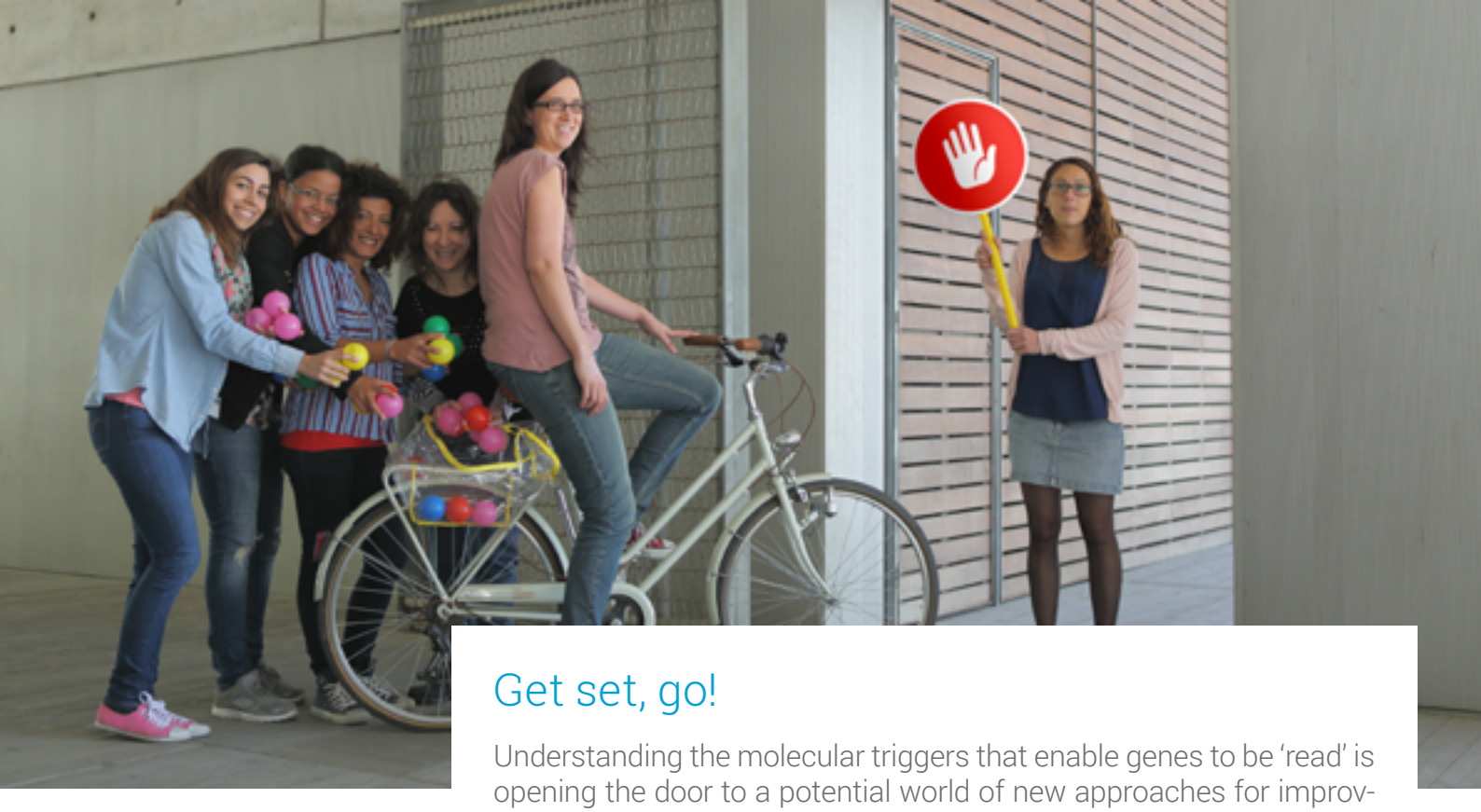
Cell Stem Cell, 17(3):300-15 (2015).



Get set, go!

Understanding the molecular triggers that enable genes to be 'read' is opening the door to a potential world of new approaches for improving life for people living with Down Syndrome.

Around one in every 1,000 babies born every year has Down Syndrome – a condition caused by inheriting an extra segment of DNA, known as a chromosome. Humans usually have 23 pairs of chromosomes, numbered one to 22 plus the sex chromosomes (XX or XY). We get one of each pair from our mother and the other from our father. But in the case of Down Syndrome babies, they end up with an extra copy of chromosome 21, meaning they have a triple dose of all the 500 or so genes on that chromosome.

It's just one of these genes – called DYRK1A – that interests Susana de la Luna, leader of the Gene Function group at the CRG. For some human genes, having an extra copy doesn't seem to matter. But the extra 'dose' of DYRK1A in Down Syndrome causes problems for cells. Similarly, if a child has only one functional copy of the gene, effectively halving the dose, they end up with an autism-like condition as well as other health issues. De la Luna and her team are trying to find out why.

GET SET

Genes are molecular 'recipes' that tell cells how to make protein molecules, which do all kinds of jobs in the body from forming strong structures like the skin to breaking down food to release energy. DYRK1A makes a type of protein called a kinase (also referred to as DYRK1A), which sticks tiny chemical tags onto other proteins and either triggers them into action or switches them off.

"We want to understand the molecular mechanisms that underlie the problems caused by three or one copy of DYRK1A," says de la Luna, "so we need to know the targets of the kinase, and what happens when there is too much or not enough of it."

The first clue came when de la Luna and her team discovered DYRK1A kinase in the nucleus of cells, where the DNA is kept. Looking more closely, they discovered DYRK1A is directly bound to DNA and its associated packaging proteins (known collectively as chromatin), homing in on characteristic sequences of DNA.

The next part of the puzzle was revealed when the researchers discovered that DYRK1A had a potent activating effect on nearby genes, strongly switching them on. And the final clue slotted in to place when they found that the kinase was 'tagging' an important part of RNA polymerase, the molecular machine that 'reads' genes when they are switched on and active, like reading a recipe in a cookbook.

GO!

In order to read a gene, RNA polymerase finds the start of the 'recipe' and waits there, loading itself up with all the proteins it needs to work properly. Then when everything is ready, DYRK1A adds its tags, providing the final trigger for the polymerase to start moving along the gene, reading as it goes.

"It was very surprising to discover that DYRK1A sits on chromatin at genes with these particular sequences in the 'control switches' near genes, and can directly tag the polymerase," explains de la Luna. "Not many kinases are known to do this."

Careful analysis revealed that many of the genes targeted by DYRK1A are involved in helping cells to grow – for example, by making energy or manufacturing more proteins. De la Luna suspects that this may help to explain why having too much or too little of it causes problems.

"In the case of Down Syndrome there are other genes on chromosome 21 with increased activity which can also contribute to cells not working properly, but we think the new role we have found for DYRK1A role has something to do with the effects we see in children with Down's or the autism syndrome."

This paper, published in the journal Molecular Cell, raises many more questions than it answers, providing a lot more work for de la Luna and her team still to do.

"Much of this work was done by Chiara Di Vona," she says, highlighting her PhD student's vital role in the study and other collaborators Nuria Lopez-Bigas and her team at Pompeu Fabra University and Stephan Ossowski's lab at the CRG.

"It was a risky project with technical challenges, but it paid off. This is a paper about basic biology, so there is still a long way to go to explain how the changes in this gene cause disease. There are also still many questions, but this work opens an exciting door to a place where there is a lot to explore and where we might find solutions to improve the outcome for people affected by these conditions."

ORIGINAL PAPER

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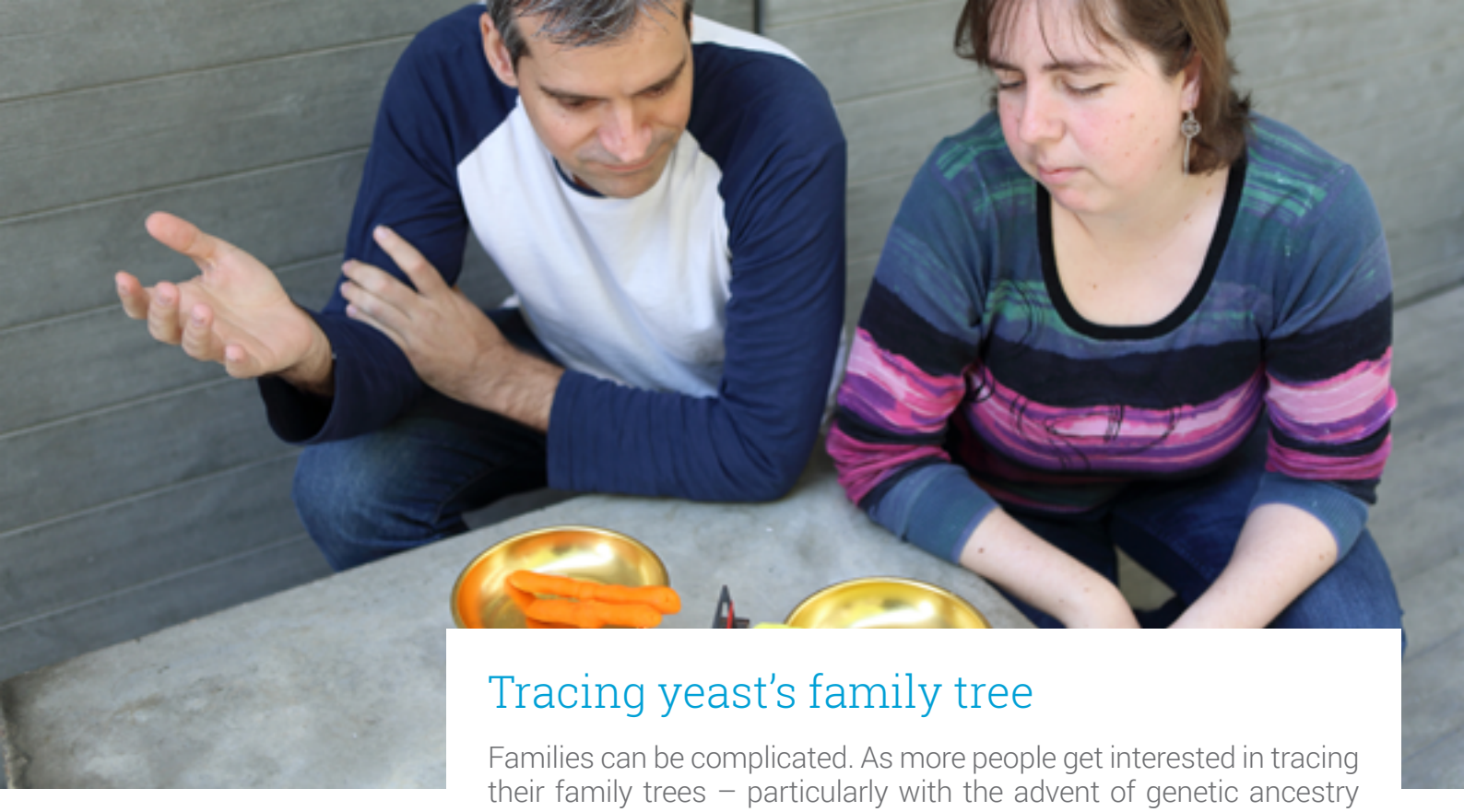

Tracing yeast's family tree

Families can be complicated. As more people get interested in tracing their family trees – particularly with the advent of genetic ancestry testing – there can be unexpected surprises lurking in the branches.

Untraceable relatives, mistaken parentage and confusing characteristics that don't make sense. And the further back in time you go, the more confusing the picture becomes. This isn't just true for human family trees. It's true for all living things, including baker's yeast (more formally known as *Saccharomyces cerevisiae*) – one of Toni Gabaldón's favourite organisms. He heads up the Comparative Genomics lab at the CRG, dedicated to understanding the complex evolutionary twists and turns that have led to the genetic makeup of the many different species we see today.

THE OFFICIAL VERSION

Baker's yeast was the first species more complex than bacteria and viruses to have all of its DNA 'read' – a process known as sequencing – back in the 1990s. Like reading the individual letters of the recipes in a cookery book, DNA sequencing enables scientists to read all the biological 'letters' that make up an organism's genes.

After poring through all the data, researchers noticed something a bit strange. In many cases there were two copies of certain genes. They weren't completely identical, but they were very similar – a bit like having recipes for both an orange and a lemon cake in a recipe book, when the only difference is the fruit and everything else is the same. But where had these extra genetic 'recipes' come from?

The proposed answer was that somehow, way back in evolution, all the genes in the yeast had copied themselves – an act known as whole genome duplication. Over time, the two copies of each gene had evolved and changed independently, so they no longer looked exactly the same. Sometimes one of the pair had been lost, while in other situations, both copies had vanished entirely. By analysing the similarities and differences between the duplicated genes across different species of yeast, scientists were able to pin this event to roughly 100 million years ago.

Yet there were some problems with this idea. As Gabaldón explains, "When we looked closely at these genes in the yeast genome, they seemed to be telling different evolutionary stories. When you look across species – for example, if you take a human gene – you would expect its closest relative would be the chimp version of the gene, then the gorilla gene and so on. And you would expect all the genes should be related to those in similar species in consistent ways." To draw an analogy with a human family tree, two sisters should be related in the same way to their parents, cousins, aunts and uncles. But this didn't seem to be the case for the duplicated yeast genes. The family stories just didn't match up – it was a genetic mystery.

THE SOLUTION: PASTE, THEN COPY

In their paper, published in the journal PLoS Biology, Gabaldón and his collaborator Marina Marcet-Houben carefully analysed DNA data from 26 different but related species of yeast. By looking at members from across this broad family tree, they wanted to more precisely pinpoint the time at which the whole genome duplication event happened.

Then they noticed something unusual. Instead of seeing evidence for the whole genome copying 100 million years ago, it looked like the duplication had occurred earlier in time.

"This should have been the perfect test for our method," says Gabaldón. "We thought we knew when the genes were duplicated, so it should have worked. But to our surprise we didn't see that – the duplications we were looking at were more ancient. At first I thought we had a problem with the method, but then we figured out what was going on."

The key piece of evidence was the fact that even though millions of years of evolution had passed, the two copies of the supposedly duplicated genes were just too different from each other to be accounted for by a simple copying process. Something else must have happened.

"We realised that these genes had come from two separate species of yeast that had joined together – we call it hybridisation," he explains. "So the genes had already diverged and become different, before they came together."

Effectively, two different yeast cells had somehow merged together, combining all their genetic material to make a hybrid with double the amount of DNA. Not only does this idea account for the earlier timepoint for the duplication that Gabaldón and Marcet-Houben found with their analysis – because these species diverged further back in time than 100 million years ago – but it also explains why the evolutionary 'stories' of the gene pairs don't match up. If the genes came from separate species that were already evolving independently, there's no reason why they should share exactly the same family histories.

Although it's a neat solution, there's one big problem: hybrids, formed by two distinct species merging together tend to be unstable and can't reproduce. Because the two sets of chromosomes are slightly different, it causes problems with meiosis – the process of making sex cells (gametes, such as eggs and sperm in mammals). During meiosis, matching pairs of chromosomes pair up, ready to be separated into individual gametes. But if the chromosomes are different, this matching process doesn't work and gametes don't form properly. This explains why mules – the offspring of horses and donkeys – are sterile and can't produce foals, and it's also true of hybrid yeast.

To solve this issue, Gabaldón thinks the ancestral hybrid yeast performed some further genetic gymnastics, duplicating its newly-merged double genome. This is the equivalent of a DNA balancing act, providing the right number of matching chromosomes to get through meiosis. Then, once a stable hybrid had formed – the ancestor of today's baker's yeast – further changes happened as genes got lost, shuffled and switched around.

This process of biological pasting (hybridisation), copying (whole genome duplication) and subsequent editing is a new way of looking at the evolutionary history of Saccharomyces cerevisiae. And it's not one that was immediately accepted by the research community.

"People were shocked!" says Gabaldón. "Scientists in the yeast world had the idea of a whole genome duplication written in stone in their minds, and it was difficult to convince some of them. There was a lot of research that had been derived from the idea that it was a simple doubling of the genome – even work from our own lab – and we all had to rethink it. But this is how science works."

This new work also throws suspicion on other species – including humans – where there's evidence that genome doubling has taken place. Gabaldón thinks that some of these events may be hybridisations rather than simple duplications, so maybe there are some genetic surprises lurking in the branches of our own family tree.

ORIGINAL PAPER

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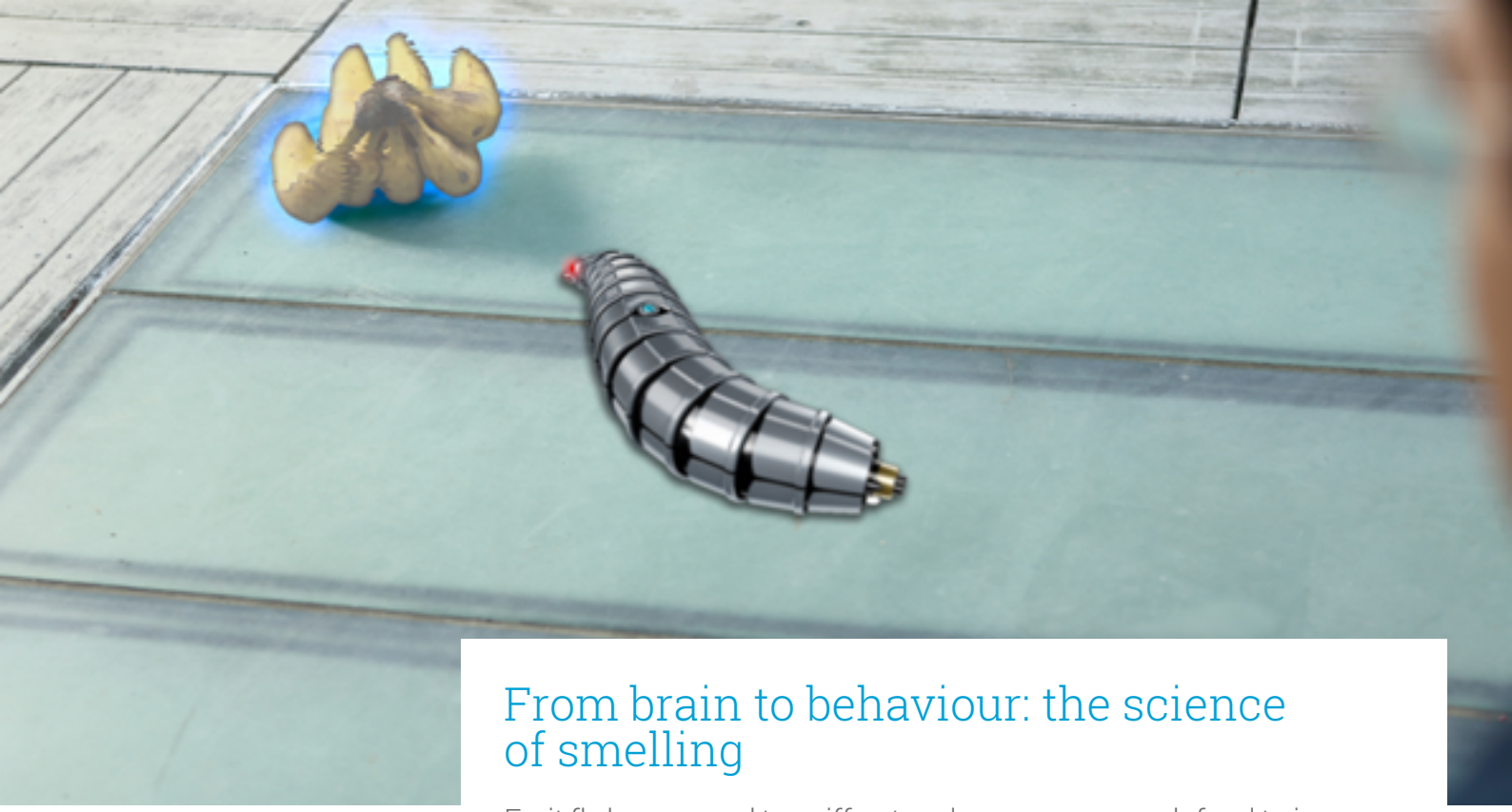
PLoS Biol, 13(8):e1002220. eCollection 2015 Aug.



From brain to behaviour: the science of smelling

Fruit fly larvae need to sniff out and consume enough food to increase their body weight by a factor of 1,000 in just six days. But how do they do it?

"Recently there was a fire in my apartment block," says Matthieu Louis, leader of the Sensory Systems and Behaviour group at the CRG. "I could smell burning plastic, and thought it must be coming from my kitchen. But when I went in there the smell didn't increase. Then I went in the hallway and I could tell it was stronger, so I knew it was coming from another apartment."

Luckily for Louis and his neighbours, it wasn't serious and the fire brigade soon dealt with the problem. But his story neatly demonstrates the exact phenomenon his lab is working on: chemotaxis. Or, to put it simply, how organisms move in response to smells.

Smell – or at least the ability to sense chemicals in the environment – is perhaps the oldest sense and it's fundamental to the survival of all living things, from bacteria finding their way towards food to animals (and scientists!) sniffing their way out of danger by figuring out the location of dangers such as predators or fire.

THE LARVA THAT TURNED

Rather than having millions of nerve cells in their noses like dogs or humans, for example, fruit fly larvae have just 21. This makes them a useful model for studying how sensory inputs from the outside world are translated into nerve impulses that control behaviour.

As Louis explains, "When you consider how they are put together, the neuronal architecture of the olfactory system is roughly the same as that which is observed in vertebrates. That's quite exciting because we have a massive reduction in the number of neurons, but you don't sacrifice the organisational principles which are there in more complex systems like humans."

This means that the larvae still respond to smells in their environment using the same logic as larger animals. They will head straight towards the source of a tasty smell when it's getting stronger – similar to a dog on the trail of a rabbit or a person in the street sniffing their way to a delicious bakery – or stop and turn from side to side when they lose the scent, in the hope of capturing it again.

"There's a loop you create between sensation – perception of the sensory stimulus – and action," Louis says. "So we're trying to predict something about the action from an understanding of the perception – how much information can the animal extract from the smells in its environment to find out where the food is located."

By carefully monitoring individual larvae in a tightly controlled environment, Louis and his team were able to see exactly how the animals responded to changes in the concentration of a delicious pineapple odour – moving quickly forward when the smell was getting stronger, and stopping and turning when it became weaker.

To simplify things even further, the scientists used larvae that had been manipulated in such a way as to have just one functional nerve cell in their nose rather than the full set of 21. Yet even with this single cell, the larvae still showed perfect responses to the pineapple smell.

The next step was to place a tiny electrode next to that nerve cell – an extremely delicate job – to measure how quickly it was firing in response to the changing odour. To Louis' surprise, he and his team discovered that there wasn't a straightforward relationship between the activity of the nerve cell and the level of the pineapple scent in the larva's environment. Instead, this single nerve cell was somehow processing how the smell was changing – something known as an odour gradient.

The researchers found that the nerve cell was firing faster when the gradient was increasing (getting stronger) and slowing down as the gradient grew weaker. In turn, fast firing meant the larva would keep running forwards, while slower signals or no nerve impulses at all were the sign to stop and change direction.

As Louis explains, "We were not expecting so much information processing already at the level of a single olfactory nerve cell. It can exactly detect how much the smell is changing during motion, and use this information to deduce whether it is moving toward or away from the source."

TURNING THE DIAL

Louis' next question was this: exactly how does nerve cell activity relate to behaviour? If different rates of nerve cell firing are related to these different behaviours, in response to varying amounts of odour, then is it possible to predict exactly how the animal will move in response to any particular level of nerve cell activity?

To answer this problem, the team used an exciting new technique known as optogenetics, where the activity of the nerve cell could be precisely controlled in response to flashes of light. By using the light pulses to make the nerve cell fire fast, slow, or at intermediate levels, the researchers created a 'virtual' odour gradient.

"This is a trick we can use," says Louis. "Through optogenetics we can create artificial sensory realities. So we could then ask if you challenge a larva with this virtual odour gradient, like it's detecting a real odour gradient, what will it do?"

Impressively, the larvae responded in exactly the same ways to these 'virtual' smell gradients as they did to the real thing. When Louis and his team made the nerve cell fire rapidly, the larva moved as if it were chasing straight after the smell of food. But when they slowed down the light pulses, making the nerve cell fire slowly, it stopped and turned. Effectively, they had developed a way to 'remote control' the behaviour of a larva by manipulating the firing of a single nerve cell.

Thanks to painstaking measurements the team was able to develop a mathematical model to describe exactly how the rate of nerve cell activation is related to behaviour, and this exactly matched up to their findings with the real larvae in the lab. Intriguingly, they also showed that there's still an element of randomness to the animals' behaviour: it's not a 100 per cent certainty that they will run forward in response to a particular level of nerve firing.

"The larva is not just a robot," explains Louis. "There is some variability, and some opportunity for it to implement its decision. But to a very large extent we were able to predict its behaviour based on the knowledge of the activity of this single olfactory nerve cell in the nose. This is the one of the first attempts to predict behaviour based on controlled olfactory input – we've been able to mathematically describe what's coming in to the olfactory nerve cells and going on to the motor nerve cells that are then implementing the actual behaviour, making it move."

ORIGINAL PAPER

Schulze A, Gomez-Marin A, Rajendran VG, Lott G, Musy M, Ahammad P, Deogade A, Sharpe J, Riedl J, Jarriault D, Trautman ET, Werner C, Venkadesan M, Druckmann S, Jayaraman V, Louis M. 'Dynamical feature extraction at the sensory periphery guides chemotaxis.' *Elife*, 4 (2015).

TRACING THE CIRCUIT

Although Louis and his team have focused on a single nerve cell, he likens his achievement to figuring out the first component in an incredibly complex electrical circuit. And this should also scale up to more complicated organisms.

"The number of nerve cells we're talking about here in the larva is around 100. But many of these processes, like detecting a change in concentration, are things that are achieved by most organisms including humans. So the chances are that the mechanisms that we're discovering here are basic principles that we think will be implemented in other organisms. That's why we're so keen on mathematical modelling – there's a logic that is common to the building of most brains."

As well as being an important scientific step forward, which the team published in the journal eLife, this project has also been a major technical challenge. It took six years and several national and international collaborations to develop the precision techniques required to measure the impulses coming from a single nerve cell in a larval brain and the optogenetic tools. But in Louis' view, this was worth it.

"My vision was to develop a model – a model that would teach us something about what's happening in the brain of the larva when it's navigating an odour gradient. This was an ambitious task, but my lab was brave enough not to shy away from those technical challenges. It took a lot of effort and being bold, and we eventually succeeded. I would say that bringing all the pieces together was incredibly satisfying – to be able to make that scientific journey – and I feel that we managed to get to the destination."

European Research Council
Established by the European Commission

ERC Researchers at CRG

STARTING GRANTS


Pedro Carvalho


Pia Cosma


Toni Gabaldón


Manuel Irimia


Fyodor Kondrashov


Manuel Mendoza


Gian Gaetano Tartaglia

CONSOLIDATOR GRANTS


Ben Lehner

ADVANCED GRANTS


Roderic Guigó


Vivek Malhotra


Luis Serrano


James Sharpe


Juan Valcárcel

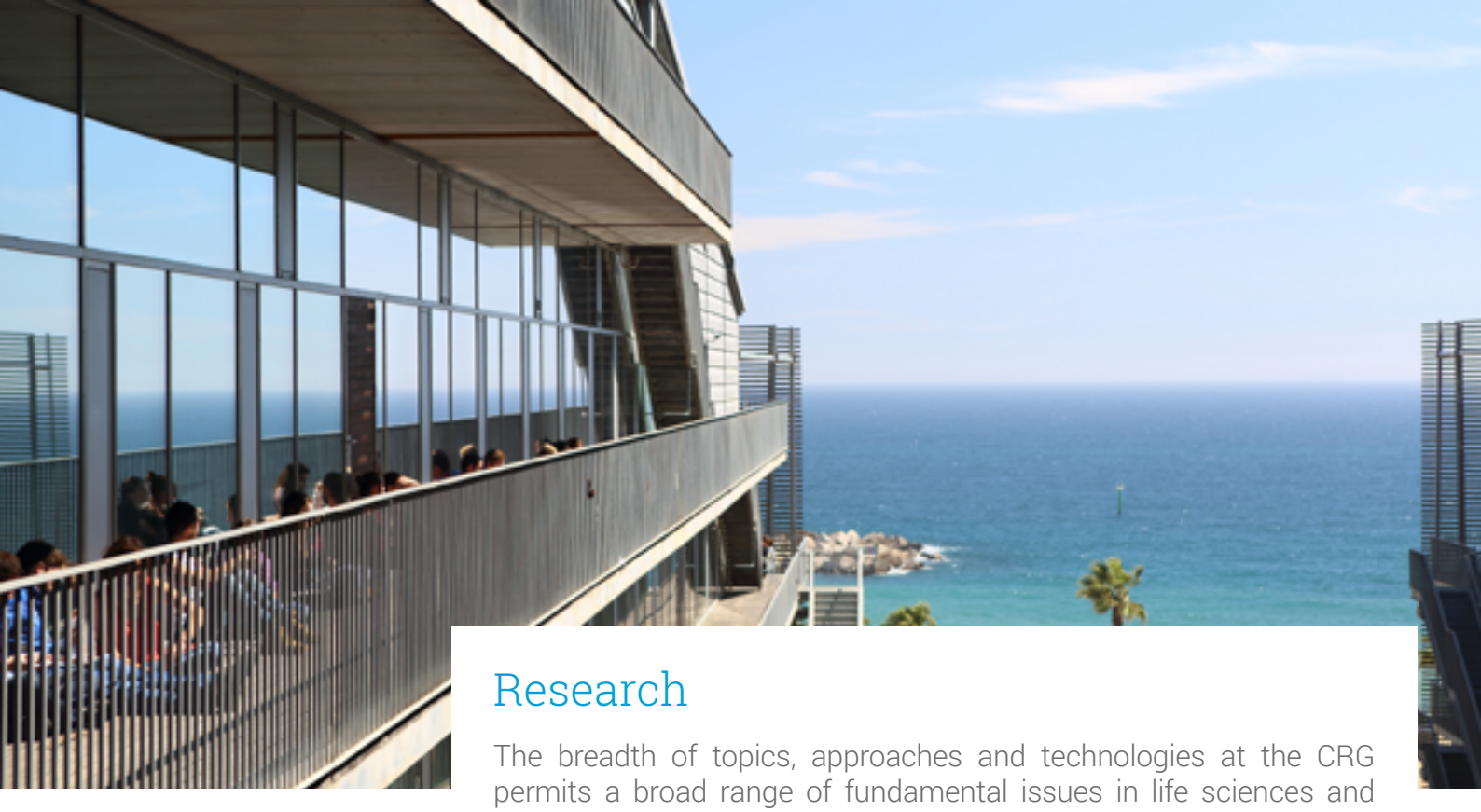
SYNERGY GRANTS


Miguel Beato


Thomas Graf


Guillaume Filion


Marc Marti-Renom (CNAG-CRG)



Research

The breadth of topics, approaches and technologies at the CRG permits a broad range of fundamental issues in life sciences and biomedicine to be addressed. Research at the CRG falls into four main areas: gene regulation, stem cells and cancer; cell and developmental biology; bioinformatics and genomics; and systems biology. Since 1st July 2015, the National Centre for Genome Analysis (CNAG-CRG) is also part of this research structure.

COORDINATOR
Roderic Guigó

BIOINFORMATICS AND GENOMICS PROGRAMME

The overarching goal of research groups of the Bioinformatics and Genomics Program is the understanding of the encoding of biological information in the sequence of the genomes (that is, the complex relationship between genomes and phenotypes), and how evolutionary forces have contributed to shape this encoding. The groups are interested in understanding the sequence patterns that instruct the molecular pathway leading from the DNA to protein sequence, and the mechanisms by which the outputs of this pathway (RNA and proteins) interact to confer functionality at the molecular and cellular levels. Research also includes the development of basic alignment methodologies tailored to functional genomic domains exhibiting specific patterns of sequence conservation, and investigation of how the evolution of these domains is correlated with the evolution of the encoded phenotypic traits. We are also interested in uncovering the very basic molecular events that govern the evolutionary processes. Last, the program aims to translate the understanding of the human genome sequence into knowledge about diseases.

The scientific highlights of the program during 2015 include the development of methods for the systematic analysis and evolutionary profiling of Long Non Coding RNAs in non-model organisms, the finding that the whole genome duplication in yeast was caused by inter-specific hybridization, the characterization of the patterns of transcriptional variation across individuals and tissues in humans, the delineation of the complex evolutionary history of Selenophosphate Synthetases, and the finding that developmentally regulated genes are transcribed in the absence of canonically activating histone modifications. The program has continued to deploy and support the European Genotype Phenotype Archive (EGA), in collaboration with the European Bioinformatics Institute (EMBL-EBI).

CELL AND DEVELOPMENTAL BIOLOGY

COORDINATOR
Vivek Malhotra

The mission of the scientists in the Cell and Developmental Biology department is to reveal the mechanisms of cell compartmentation, division and tissue organisation. The department is staffed by Vivek Malhotra (mechanism of protein secretion), Isabelle Vernos (microtubule and spindle dynamics), Manuel Mendoza (cytokinesis, chromosomal segregation, and cell cycle check points), Pedro Carvalho (organelle biogenesis and homeostasis), Jerome Solon (tissue organisation), and Sebastian Maurer (cytoplasmic RNA localisation). Vivek Malhotra, Manuel Mendoza and Pedro Carvalho are funded by grants from the European Research Council (ERC). Pedro Carvalho is also a recipient of the international early career scientist award from HHMI and in 2013 was elected EMBO Young Investigator. Isabelle Vernos is a member of the Scientific Council of the ERC and is also a member of the Advisory Council for Science, Technology and Innovation of the Spanish Secretariat for Research, Development and Innovation.

The department published a number of highly important papers in 2015. But the publication of Jerome Solon and colleagues merits special attention (Salas et al, Dev. Cell 2015). These authors showed that during development in drosophila, more specifically in stages leading to dorsal closure, a group of cells decreases its volume following the activation of apoptosis to generate contractile forces that drive epithelial closure. Because the decrease in cell volume is a hallmark of apoptosis, such a force generation mechanism is likely to be active in processes undergoing massive apoptosis such as brain or limb development or wound healing. These findings make for a conceptual advancement, and suggest a need to reveal full three-dimensional analysis of the process and not focus purely on the classically-performed description of apical surface remodelling.

GENE REGULATION, STEMS CELLS AND CANCER

COORDINATOR
Juan Valcárcel

Scientific highlights of groups in the program during 2015 include several important publications on chromatin structure, mechanisms of transcription, epigenetic modifications during cell differentiation and reprogramming, and networks of post-transcriptional gene regulation.

Work in Pia Cosma's group in collaboration with the group of Melike Lakadamyali (Institute of Photonic Sciences – ICFO) used super-resolution fluorescence microscopy to reveal that nucleosomes, the units of DNA packaging in eukaryotic cells, are distributed in clutches rather than closely packed in the classical textbook "chromatin fibres". Furthermore, the density of the clutches correlates with the differentiation status of cells, indicative of regulatory mechanisms and functional relevance. In recognition for this piece of work, Pia received the 2015 Barcelona City Prize.

Work in Susana de la Luna's group revealed a novel function for the Dyrk1A kinase, an important protein encoded by a gene located in a region of Chromosome 21 linked to Down Syndrome. The new data revealed that Dyrk1A is part of transcriptional complexes, associates with a specific subset of promoters and is involved in phosphorylation of the Carboxy-Terminal-Domain (CTD) of RNA polymerase II, a modification important for transcription activation and elongation. These findings open a new perspective to consider the targets and effects of Dyrk1A and other kinases in both normal cell function and in disease.

The long-standing efforts of Luciano Di Croce's lab to understand the function of one of the key transcription repressor complexes, Polycomb, produced unexpected results in 2015. They found that the Mel18 subunit of the complex engages in interactions with distinct sets of other proteins and, as a consequence, deploys transcriptional regulation programs that include both repression and activation of genes relevant for differentiation of stem cells into cardiac cells. These results reveal the dual activities of the Polycomb complex and its implication in mesoderm lineage differentiation, of relevance for future developments in heart regeneration.

Collaborative work between the groups of Thomas Graf and Miguel Beato revealed that the transcription factor C/EBP, which can promote trans-differentiation of B cells into macrophages, does so by activating both pre-existing and de novo transcriptional enhancers important for macrophage differen-

tiation. These results are of relevance because they provide clues about the hierarchy and kinetics of gene activation required for swapping between cell fates as well as ways to short-cut these decisions.

The Valcárcel group carried out the first genome-wide screen for alternative splicing regulators of an endogenous gene (the Fas/CD95 receptor) in mammalian cells. The results revealed connections between the splicing process and transcription, signalling pathways and other cellular processes, including iron homeostasis. Systematic analysis of the effects of depleting each component of the spliceosome allowed the reconstruction of the network of their functional relationships. This revealed that splicing regulation can occur at essentially every step of the complex process of spliceosome assembly and also offered a new tool to explore mechanisms of post-transcriptional gene regulation. These approaches will be expanded through collaboration with the CNAG-CRG and the support of a European Research Council grant.

COORDINATOR

James Sharpe

SYSTEMS BIOLOGY

The research groups in the Systems Biology program cover a wide range of topics: from dynamic gene regulatory networks to systems neuroscience, and employ a wide range of model systems to address these issues, including prokaryotes, cell lines, *C. elegans*, *Drosophila* and mice. Underlying this diversity, however, are the common goals of combining systematic and quantitative data collection, using computational models, going beyond molecular descriptions and arriving at a deeper dynamic understanding of complex biological processes. To achieve these goals the program is strongly interdisciplinary, comprising a high proportion of physicists, mathematicians and computer scientists, in addition to biologists. In this way the program tackles topics such as: signal transduction, gene regulatory networks, multicellular patterning, chemotaxis, systems neuroscience, the evolution of networks, and the impact of stochastic noise at the whole organism level.

The program pursued various activities during 2015, including the 5th edition of the popular Systems Biology Summer School in June - again teaching the basics of dynamical modeling to a group of 22 internationally-selected young researchers. This year also saw the departure of one of our Junior Group Leaders – Johannes Jaeger. After 7 years in the program combining experimental work with computational modeling, to understand the detailed dynamics of molecular patterning in the early *Drosophila* embryo, Yogi left the CRG in September to take up his new position as director of the Konrad Lorenz Institute (KLI), in Klosterneuburg, Austria. We wish him well in this new adventure!

Scientific highlights of the year covered a variety of topics. The group of Matthieu Louis revealed how neurons in the Drosophila larva extract information about external odor gradients to guide chemotaxis, while Mara Dierssen's group showed that the drug epigallocatechin-3-gallate (EGCG), when used in combination with environmental enrichment, could reduce symptoms in a mouse model of Down syndrome. Luis Serrano's team provided further insights into gene regulation and virulence in the bug *Mycoplasma pneumonia*, while the lab of Ben Lehner discovered that the differential rates of variation across the human genome are due to differences in DNA repair rates rather than differential mutation rates, and the group of Manu Irimia revealed the influences that alternative splicing can have on development and evolution. And finally, the first successful attempt at reverse-engineering the structure of a gene regulatory circuit on a growing domain was achieved by the group of James Sharpe.

CNAG-CRG

DIRECTOR

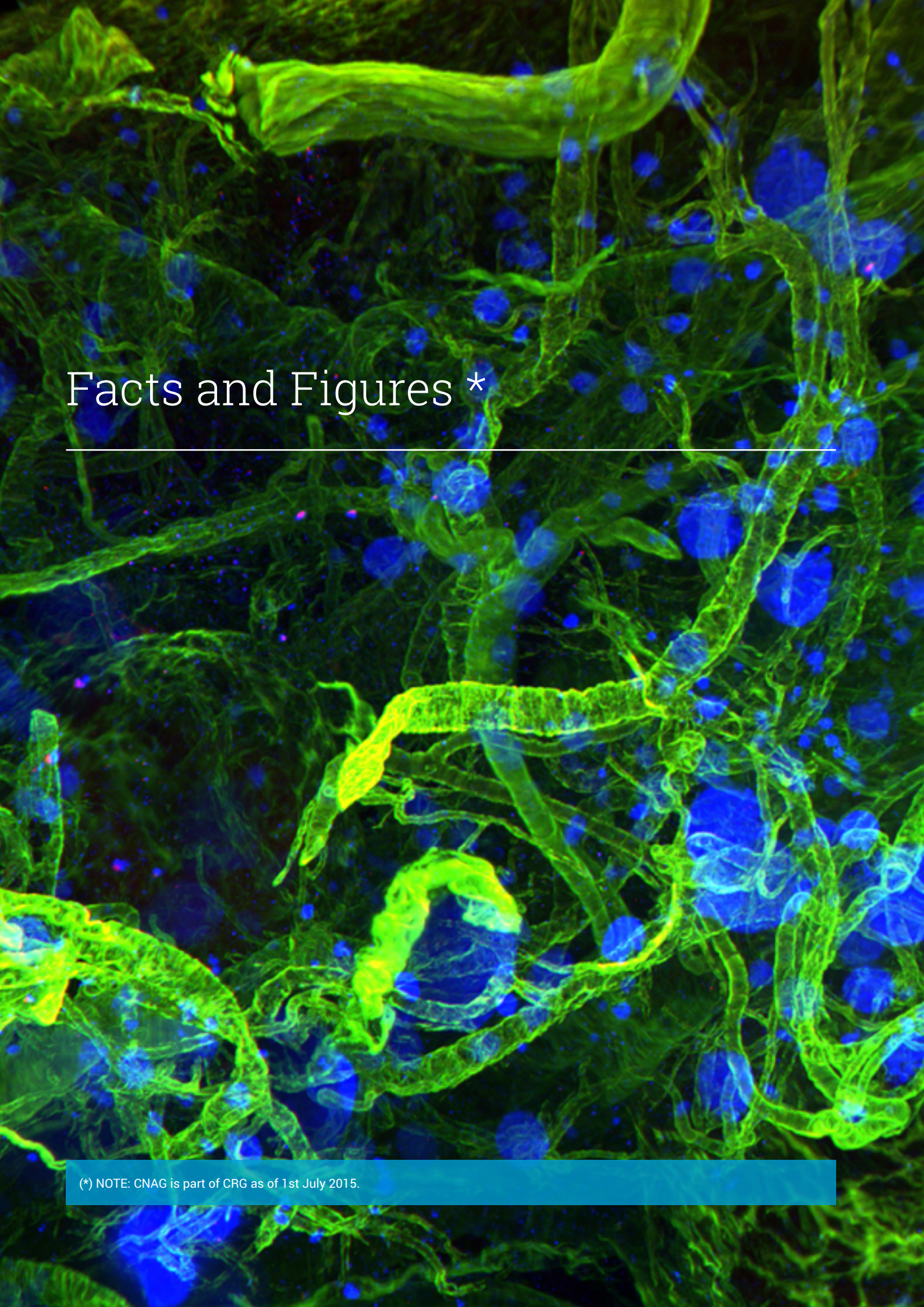
Ivo Gut

The year 2015 has been another productive and successful one for the CNAG-CRG, which has also undergone major changes. The administrative move to join the CRG will provide stability, and formidable opportunities to strike synergies and strengthen our research ties. Internally, we have broadened our areas of research with the incorporation of the Population Genomics team led by Oscar Lao and, with the arrival of Holger Heyn, our Single Cell Genomics team has gained a new leader.

The CNAG-CRG has consolidated its role as a high-quality collaborator in many aspects. Several of our large-scale international projects, the EU-funded project Blueprint of the International Human Epigenome Consortium and the International Cancer Genome Consortium project are nearing their conclusion and we have been instrumental in generating the high quality data necessary for the remarkable findings of the Spanish CLL-ICGC project that have been received with great acclaim by the international research community. We have taken a leading role in the ICGC publication in *Nature Communications* that summarizes the effort of 83 researchers from 78 institutions to create reliable standards to obtain accurate results in the detection of somatic mutations, which are a hallmark of cancer genomes.

In preparation for large-scale clinical and population-based projects we have increased our computing infrastructure to 3,500 computer cores which provide 200 TFlops, and 7.6 petabytes of data storage. There is capacity enough to hold all of the sequencing data produced at CRG-CNAG and it is used by our bioinformaticians to deliver high quality results. At the same time, we have been working hard on the quality, performance, efficiency, and integration of our processes and computing. We have further developed our quality system for the entire process from sample reception, to laboratory and data analysis.

In 2015, we started B-CAST, a large-scale EU-funded project, to characterize the tumours of 10,000 breast cancer patients. This multi-year project will generate a unique opportunity to relate background genetic profiles and cancer-specific somatic mutations with treatment outcomes.



Facts and Figures *

(*) NOTE: CNAG is part of CRG as of 1st July 2015.

Publications

Total Publications

193 CRG

210 CRG+CNAG

Average Impact Factor

8.46 CRG

8.61 CRG+CNAG

1st Quartile Publications

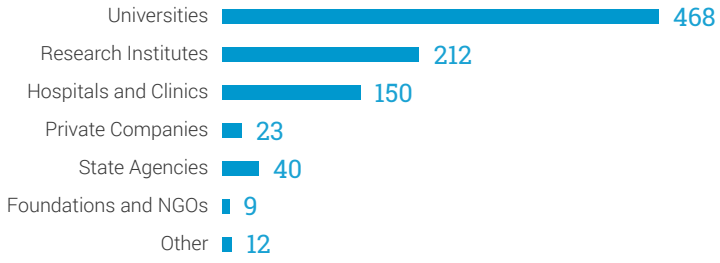
82% CRG

84% CRG+CNAG

CRG Publications with Impact Factor above 10 (April 2016)

32

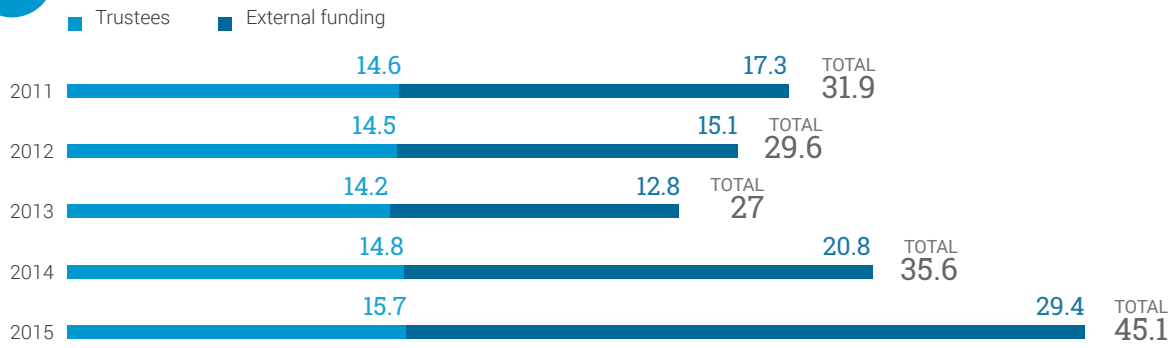
Collaborations by type of collaborating institution



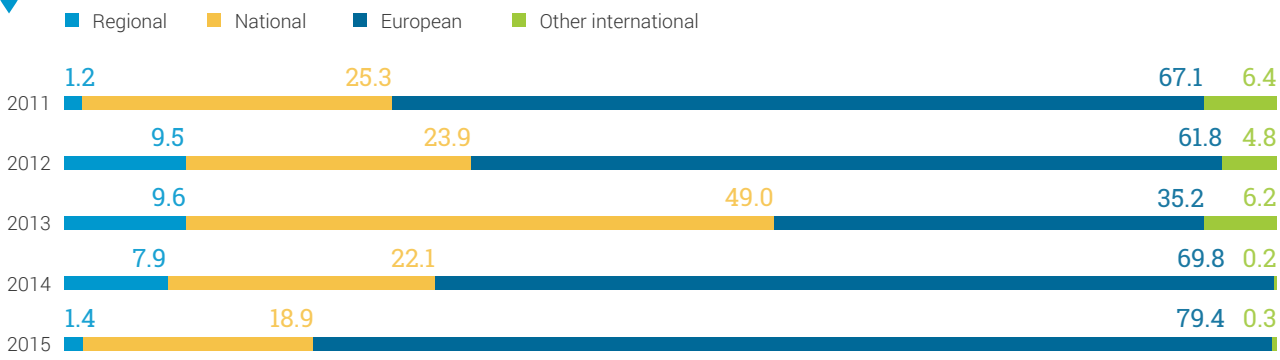
Budget

Total (2015)	CRG	CNAG
€45.1 Million	€36.4 Million	€8.7 Million

Funding Evolution in M€



External Funding by Origin (%)



EU Coordinated Projects

Ongoing Projects

4

New Projects

4

Total budget (8 projects)

> €35 Million

Total CRG budget (8 projects)

> €8 Million

Participating Institutions

58
(including 17 industrial partners)

Personnel

Total

530* CRG: 462 CNAG: 68

(*) FTE, full-time equivalent: 507,6

Research Staff

463* CRG: 400 CNAG: 63

(*) FTE, full-time equivalent: 444,1

Suport Staff

67* CRG: 62 CNAG: 5

(*) FTE, full-time equivalent: 63,5

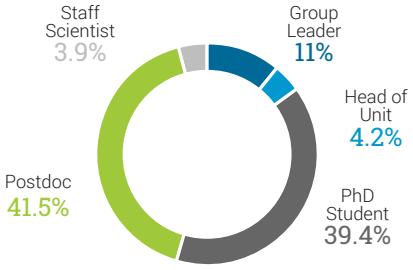
Women

50.4%

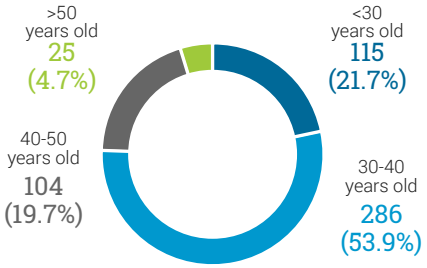
Men

49.6%

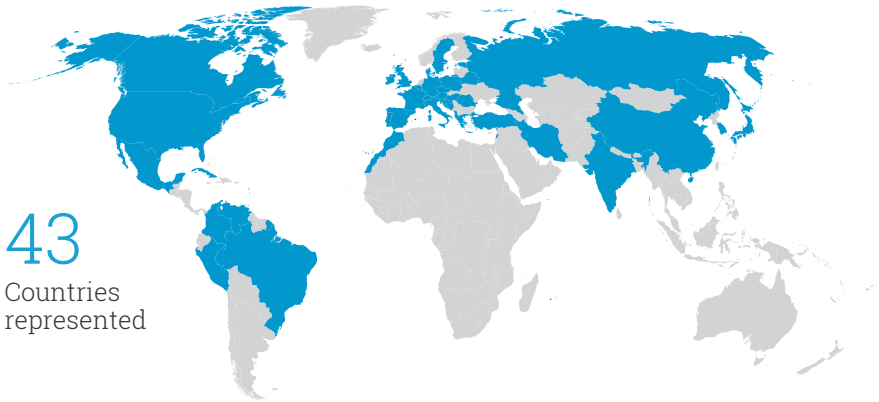
Research Categories



Age



Internationality



43
Countries represented

60.5%
Group Leaders

58.5%
PhD Students

69.2%
Postdoctoral Researchers

62.7%
Total Research Staff

Advanced Training

PhD Theses defended
14

Courses@CRG
10

CRG Coach
11 (internal career development courses)

CRG STAR
1 (Bio-Business School)

Events

International meetings
12

High-profile seminars
148

Technology & Business Development

Reported Inventions
14

Patent Portfolio
10

Agreements with companies
11

Total Income
€ 511,068

Communications, Public Engagement and Science Education

Media Relations

Media Appearances
2,503

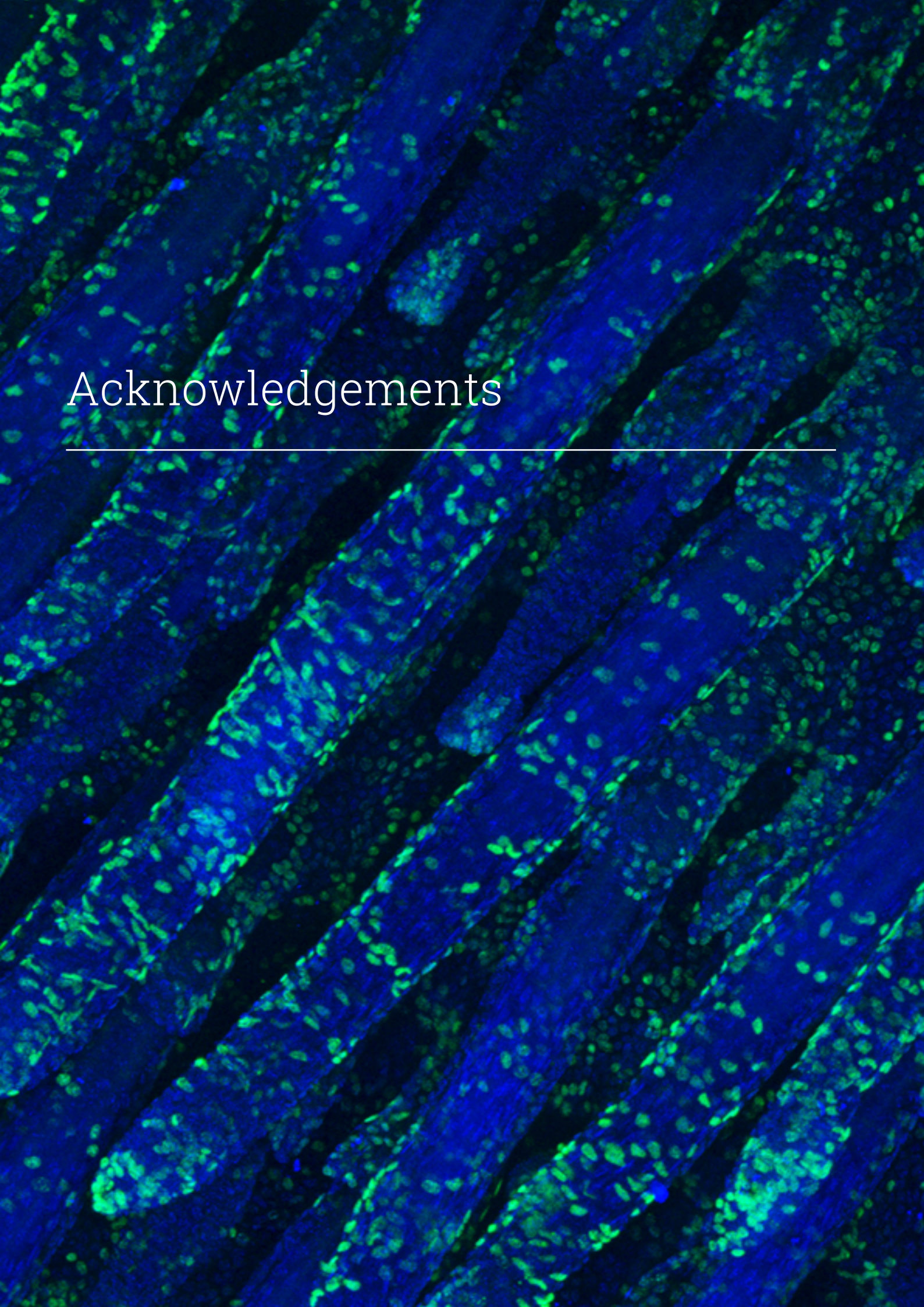
Value of Media Appearances
€ 9,162,516.13

Public Engagement and Science Education

Activities Organized
202

Audience Reached
13,942

Schools & Students: 5,954
Teachers: 181
General Public: 5,807



Acknowledgements

The support from our trustees, public and private funders and sponsors is key to accomplish CRG's mission to discover and advance knowledge for the benefit of society, public health and economic prosperity.

Trustees

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Private Funders

OBRA SOCIAL "LA CAIXA"

"la Caixa" foundation supports several key initiatives at the CRG, such as its International PhD Programme since 2008 and additional scientific and outreach activities since 2014: the partnership between the CRG and the European Bioinformatics Institute (EMBL-EBI) to jointly run the European Genome Phenome Archive (EGA) and the CRG's first citizen science initiative 'Saca la Lengua' (Stick out your tongue).

AXA RESEARCH FUND

The "AXA Chair in risk prediction in age-related diseases" was created in 2014 for a period of 15 years with a 1 million-euro endowment. Dr. Ben Lehner was appointed the first chair holder to further his work in the development of personalized medicine to better protect individuals against the unique risks they face in diseases such as cancer.

NOVARTIS

Novartis engages in extensive collaboration with the CRG. Since 2003, the company has supported the organization of CRG Annual Symposia and backed an annual fellowship for postdoctoral researchers in the field of genomics from 2004 to 2012. A new mobility programme CRG-Novartis-Africa was set up in conjunction with the University of Witwatersrand (Wits) in 2012. The programme currently includes other research institutions and universities in Africa and allows three excellent late-stage PhD students or early-stage Postdoctoral fellows to do research and continue their training at the CRG for six months every year.

FUNDACIÓN BOTÍN

Fundación Botín, through its area of Science and in collaboration with the Technology and Business Development office at the CRG, promotes the translation into the market of research results produced in the labs of Dr. Juan Valcárcel (currently) and Dr. Luis Serrano (2007-2013). They do this by providing economic and management resources to identify promising ideas and results early, assessing their potential and best mode of protection through intellectual and industrial property rights, and finding the necessary technology and industry partners or investors to help technologies or products move forward into the market for the final benefit of society.

FUNDACIÓN RAMÓN ARECES

The Ramón Areces Foundation provides three-year funding for a highly talented young postdoc to carry out research at CRG. The successful postdoc, selected from a competitive call, is currently Xianghua Li, who works in Dr. Ben Lehner's lab.

FUNDACIÓ BANC SABADELL

The Banc Sabadell Foundation provides support to the CRG's traveling scientific picture exhibition launched in 2013 **"TREE OF LIFE. The complexity of life: from the cell to a living organism"**. It was first shown in Alella, near Barcelona, then in Alicante and Barcelona (Palau Robert) in 2014 and on the premises of the Government of Catalonia Delegate's Office of Girona in 2015. The exhibition has also been on display as part of the celebration of "Researcher's Night" in Barcelona (CCCB) and during Open Day at the Barcelona Biomedical Research Park. Overall, the exhibit has received over 20,000 visitors.

FUNDACIÓ CATALUNYA-LA PEDRERA

Fundació Catalunya-La Pedrera supports vocational training activities for young talented students to nurture their interest in science and pursuit of a scientific career. Key activities include scientific summer stays at MónNatura Pirineus and at the CRG, where the students take part in sessions and events focused on scientific topics with the aim of eventually proposing and developing their own project idea.

FUNDACIÓ MARATO TV3

The Fundació Marató TV3 funds six research projects led by CRG investigators related to different editions of the telethon: three projects from the 2012 edition on 'Cancer' (Thomas Graf, Pia Cosma and Susana de la Luna), two projects from the 2013 edition on 'Neurodegenerative diseases' (Fátima Gebauer and Luciano Di Croce) and one from the 2014 edition on 'Heart disease' (Gian G. Tartaglia).

WORLDWIDE CANCER RESEARCH (FORMERLY AICR)

Worldwide Cancer Research is a charity which fund research into any type of cancer anywhere in the world. At the CRG, WWCR is currently supporting Bill Keyes' initiative to investigate the role of the chromatin remodeler Lsh in skin cancer (2015-2018).

BANCO SANTANDER

Banco Santander funds a joint project shared by the CSIC, the Royal Botanical Garden in Madrid, and the CRG (Toni Gabaldón), which aims to sequence the DNA of the olive tree for the first time.

FONDATION JEROME LEJEUNE

The relationship between CRG and the Jerome Lejeune Foundation began many years ago. They provided support to several of Mara Dierssen's research initiatives linked to the identification of molecular and genetic bases in several pathologies accompanied by mental retardation: Rett Syndrome, Fragile-X Syndrome, William-Beuren Syndrome and Down Syndrome. Dierssen was also the recipient of the international Sisley-Jerome Lejeune award, in its first edition in 2010. More recently, they awarded a grant to Eduard Sabidó's project on the elucidation of the mechanism of action of epigallocatechin-3-gallate as a therapeutic agent on the cognitive phenotype in Down Syndrome mice models (2015-2017).

AECC

The Spanish Association Against Cancer (AECC) has supported a number of research projects and initiatives of CRG scientists over the years. In 2015, Pedro Vizán (in Luciano Di Croce's lab) was awarded the AECC Oncologic Research Fellowship, for a 3-year project that seeks to identify and 'attack' stem cells involved in cancer.

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annualreport2015.crg.eu

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