CANCER PATHWAYS

Drosophila as a model system to study cancer
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Cancer is one of the leading causes of death in Europe and worldwide. Although significant advances have been made in cancer research, it still remains a public health concern with a survival rate of about 50 percent. It is therefore of great importance to develop new and specific drug treatments for cancer. The EU collaborative project CancerPathways combines scientific expertise of eight partners to produce fundamental advances in our understanding of cancer biology and how this disease can be attacked.

Tumour development is characterized by the uncontrolled growth of cells. Cells are constantly exposed to signals from surrounding tissues that determine whether they divide, differentiate or die. Inside each cell, signal transduction pathways forward and convert these signals, thus controlling the ultimate decision, whether they can divide – or not. Consequently, the deregulation of diverse signal transduction pathways has been linked with carcinogenesis. Although new therapeutic approaches in cancer treatment target signaling pathway components, the full potential of signaling molecules as therapy targets remains to be explored.

The CancerPathways consortium aims to identify novel targets and drug-like molecules for therapeutic application. In this respect we make use of the high evolutionary conservation of most oncopathic pathways with Drosophila representing a particularly powerful model system for the analysis of signaling cascades. The project integrates recent technological advances, such as genome-wide RNAi and compound screens in cell-based and in vivo models as well as computational approaches.

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Flies and Fate

Sarah Palin might be a little surprised to learn that she has thousands of genes in common with the fruit fly. Yet for this very reason flies are key to understanding many human diseases. For more than a century scientists have been using *Drosophila melanogaster* as a tool to better understand biological development. This work has fuelled many major breakthroughs in the treatment of human diseases including cancer.

“Although the public is often amazed that we use insects to try and understand human cancer,” says Maria Dominguez (Institute for Neurosciences, Alicante, Spain), “*Drosophila* is like the Rosetta Stone that helps us to understand the language of different genomes. A simple genome (fly) can teach us a lot about complex genomes (humans).”

Fly-biologist, Buzz Baum (Laboratory of Molecular Cell Biology, UCL, UK) elucidates: “A gene called *Lethal giant larvae* (*Lgl*) was discovered through genetic screens on flies in the seventies. No one had yet found a gene that quashed the growth of tumours in any animal. Flies born with mutations in *Lgl* get bigger and bigger and then die because of unregulated cell growth. Human versions of this and other tumour-suppressor genes play a role in cancer.”

So how do mutations in the fly gene *Lgl* lead to cancer? “Curiously, fly tumour-suppressor genes like *Lgl* don’t directly control cell growth, division or death, the usual suspects we think about when considering cancer. Instead *Lgl* controls cell polarity. This is one of the most basic properties of normal cells. Cell polarity determines, which is the top and which the bottom of a cell. This is the first thing to go wrong when *Lgl* is lost,” confirms Buzz.

“Why is cell polarity so important for the prevention of cancer? Cells in healthy tissue must be polarised in order to communicate properly; so that each cell grows and divides on schedule. On the other hand, tumours are ugly, disorganised clumps of cells confused about their polarity and unable to understand each other. Losing normal cell controls can lead to unregulated tissue overgrowth and cancer.”
We take an architectural perspective in the lab,” says Buzz. “Cells are abstract information-processing machines, but they are also physical machines, like hoovers or cars. We’re not just interested in the circuitry, the controls. We also want to know how information can induce shape changes. And how cell shape affects information processing by cells. Because cancer cells are physically very different from normal cells, the answer(s) to these questions might provide new leads for treating cancer.”

“For example we recently showed that ‘soft’ cells have problems dividing. Before normal cells divide into two they ‘round-up’ and become rigid spheres. They actually get quite stiff. Sometimes when there are problems with the genes that control cell mechanics, the cells remain soft and flat.

When soft cells divide their faulty mechanics mean that chromosomes are not equally shared between daughter cells. This process, called genomic instability, can contribute to cancer progression, so we’re now hunting for genes that control the physical properties of cells as potential targets of tumour diagnosis and therapy.”

How do you do that? “We use a technique called RNAi (see Tools and Technology) to silence genes in fly cells that we culture in dishes. If silencing a gene changes the cell shape and/or cell mechanics we then need to investigate what it does when cancers initiate in flies.”

“Cancer cells are physically very different from normal cells. Normal cells that have just come out of a human are very sensitive to their environment. You can literally see them spreading out and feeling the surroundings. Cancer cells by contrast are oblivious to their environment. This means they can grow and divide in different tissues despite external signals.”

So how can your research translate into the clinic? “We will look for genes that specifically control the shape of dividing cancer cells but not normal cells. If we can find drugs that inhibit their activity, then maybe we can pave the way towards the development of a new cancer therapy.”
A magnificent orchestration of signaling pathways interweaves to direct development from fertilized egg cell to adult. The same pathway components – proteins that convey external signals to the genome in the cell nucleus – exist in most animals. So understanding how signaling pathways work in flies is relevant to humans. While such pathways instruct development, when overactive or active in the wrong tissue, they can lead to cancer.

Technological advance now means scientists need no longer study cancer-risk genes one at a time. New techniques facilitate the analysis of entire gene networks and the way their protein products interact. “We’re trying to create profiles of many different genes in parallel,” explains Michael Boutros (German Cancer Research Center, Heidelberg, Germany), who is co-ordinating the EU-funded Cancer-Pathways network project in a bid to uncover new drug targets.

Michael introduces the metaphor of transport and trafficking to explain his research. “Consider a complex public transport system. When trains or information get blocked, the whole system is affected. Stopping trains at certain stations may impact more strongly on the network than blockages elsewhere. We’re trying to find all these critical points in cell systems where, if blockage occurs, the greatest impact is felt.”

**Signal activity**

“One of the signaling pathways we’re particularly interested in is called Wnt, says Michael Boutros. “The pathway operates inside the cells of most organisms from worms to man, so we’ve learned a lot from flies. Signaling pathways usually regulate the processes of growth and cell specialisation but they can lead to over-proliferation of cells when messed up.”

“For example Wnt signaling, when over-activated, leads to colorectal cancer. In the colon a lot of cells are constantly shed and replaced. Certain types of stem cells replenish the lining of the colon. Wnt activity in this tissue is high because it helps to regulate the process of making new cells. However, mutations in Wnt components can occur causing the
pathway to over-activate, which leads to colon cancer.”

“A mutated Wnt component can alter the activity of the pathway. In principle, we could target the mutated component or other components that act subsequently in the pathway with a drug. However a lot of these signaling pathways interweave, which is important if you want to design a drug against a signaling factor that is part of two or three different signaling routes. Unwanted side effects could result for this reason. We don’t know much about that yet.”

“We’re still surprised about how much we don’t know, because we find many things that previous genomic screens have not described. In one of the RNAi screens we did, we found a component that is specifically required for Wnt proteins to leave the cell, but it’s not required for the exit of any other protein.”

Signaling pathways keep fundamental processes in order during development. They have different roles in different tissues, so when they go awry the effects are unpredictable. For this reason, they are implicated in many different diseases. For example, Wnt signaling plays a role not only in the onset of colon cancer, but breast cancers and cancers of the nervous system.

Notch it up or down?

Maria Dominguez works on a related signaling pathway called Notch. “Notch is very important in development as well as in adult tissue,” she says. “This pathway plays a role in the growth of solid tumours in the breast, prostate and pancreas, but also in leukemia.” Cancer of the blood involves overcrowding of bone marrow with abnormal cells that can spill over into the bloodstream and spread throughout the body.

As with other pathways, Notch involves detection of signals by a protein receptor on the cell surface. This receptor internalizes the signal and feeds it through to the cell nucleus, where it activates genes controlling self-renewal, proliferation and programmed cell death. Mutations in Notch components can lead to overactive or reduced signaling and subsequently cancer.

Learning about Notch has prompted a series of clinical trials with drugs that quash the pathway. Gamma-secretase inhibitors (GSIs) have been used to this end with varying success, “But the enzyme they inhibit plays a role in more than just the Notch signaling pathway,” explains Maria, whose team of researchers and collaborators at the University of Columbia recently confirmed that quashing Notch with GSIs is not a foolproof therapeutic strategy for leukemia.

“Notch is not only important in cancer. It plays a role in cardiovascular and neurodegenerative disease. Notch tends to be over-active in cancers, but reduced in degenerative diseases. GSIs were
originally developed to treat Alzheimer’s,” says Maria. They inhibit the build up of amyloid plaques in the brain by hampering the role of a different enzyme, but they affect Notch signaling, too.

So what new cancer therapies can we expect in the next decade? “What has become easier in the last year is more precise diagnostics”, reassures Michael Boutros. “With reference to signaling pathways there are many ways to cause cancer in a cell. That’s a lead for the future and therapy will become much more individualized applying drugs to damaged signaling components on a case-by-case basis.”

New tools: RNAi

“Technology has been a key determinant of the trajectory of human history,” says Barry Thompson (Cancer Research Institute, London, UK). "As soon as there’s a new technology, society has to adjust to it and its ethical implications. With genetic modification (GM) technology, people are concerned because they don’t understand how it works. Other fears arise from the religious belief that GM is like playing God. However, it is just like any technology and can be used for good or bad purposes.”

GM encompasses a range of technologies that are used to alter the characteristics of living organisms. This may involve the insertion of new genes not normally possessed by an organism into its genome, thereby creating a transgenic animal. Genes may also be knocked-out through mutation. Recently, however, it has also become possible for genes to be ‘knocked down’ rather than ‘knocked out’. This involves blocking a critical function of cells: protein manufacture.

In order for a cell to do its job, an army of proteins must be created from DNA templates stored in the genome. Yet, DNA (deoxyribonucleic acid) is not the only coding material inside our cells. Making protein requires RNA (ribonucleic acid) templates that faithfully mirror DNA sequences. Single-strands...
of RNA are assembled along the length of DNA. Such so-called messenger RNA (mRNA) then leaves the cell nucleus and travels to the protein-making factories of the cell. Blocking RNA hampers protein manufacture, blocking expression of the gene in question.

**“Now we can silence any gene in the genome with reagents that we design from scratch.”**

Within the past decade scientists have been uncovering the natural ways and means that cells regulate gene expression. RNA interference (RNAi) was discovered because of the responses a cell has to viral infection. Viruses often possess a double-stranded RNA genome. “This is different from the single-stranded RNA normally present in our cells,” explains Barry. “Luckily our cells recognize the double-stranded viral RNA and initiate a program of RNAi to destroy it.”

In 2006, Andrew Fire and Craig Mello were awarded a Nobel Prize for describing how RNAi works in worms. “Researchers now employ the technique to silence genes by making double-stranded RNA versions of them and expressing these in cells. Although it’s still not fully understood,” says Barry, “it clearly involves destruction of the normal messenger RNA, thereby blocking the conversion of DNA to protein.”

Double-stranded RNA only triggers the disintegration of mRNA with the same sequence. "The double-stranded RNA gets chopped up into small pieces, called small interfering RNAs (siRNAs)." These coding fragments become embedded in a protein complex called RISC, helping it to target the right mRNA, which RISC then degrades.

siRNAs were first discovered in plants by David Baulcombe’s group at the John Innes Centre in Norwich. Later Thomas Tuschl (Max Planck Institute, Göttingen) showed that custom-made synthetic siRNAs could induce RNAi in mammalian cells. Now, the technology is being widely used in basic science as a method to study the function of genes with the possibility of novel therapies in the future.

“Now we can silence any gene in the genome with reagents that we design from scratch,” affirms Michael Boutros. The way this affects a cell will reveal something about the gene function. “RNAi screening will help us to uncover components of signaling networks that are important in cancer so we can find potential drug targets.”

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Simultaneous snapshots

“We are building an overall picture, a bit like a railway map,” explains Michael Boutros. “We know where the tracks go through, but there are a lot of blanks to fill in, like which factors affect the whole system. In terms of methodology, we take lots of different snapshots of the system in a rapid manner. So we hope to identify critical intervention points simultaneously rather than one by one. We call this high-throughput screening.”

Custom designed siRNAs are applied to cells in tiny wells on a microplate. Microplates contain hundreds of wells and so many different siRNAs can be applied across a plate to the same cell types. ‘Knock down’ experiments can thus be run simultaneously for many genes. The activity of a particular pathway can be estimated by measuring the expression of certain target genes.

Now that it is possible to run thousands of experiments simultaneously, new techniques are required to organise and analyse the huge amount of data generated. The results are organised into a database structure. A variety of mathematical algorithms may then be applied to reveal meaning from the data. The development of computational and statistical techniques to this end encompasses the field of bioinformatics.

The CancerPathways network is focused on making high-throughput RNAi screening more feasible. As Michael explains, “We’re using RNAi as a tool to switch off genes and identify components of signaling pathways.”

High-throughput screening allows a researcher to quickly conduct millions of simultaneous experi-
“Cancer is extremely complex. It is not one disease, but many different manifestations of a similar problem. Studies in animals like flies may shed light on the molecular basis of human cancers.” Many human cancer-risk genes were first identified in flies.

networks are implicated in cancer biology, the search for small-molecules that can influence protein components of such pathways is a valid pursuit.

In a similar fashion to the high-throughput techniques outlined (see Simultaneous Snapshots) the effects of drug candidates on proteins can be assessed using micro-array technology. Recent advances in laboratory automation coupled with the ability to assemble and manage large libraries of drug candidates, mean that scientists can now screen hundreds of thousands of small molecules to see if they will affect target proteins.

Once cancer-risk genes have been found, drug candidates can be tested. Drugs normally take the form of molecules that are small enough to traverse the cell membrane and interact with specific proteins by hampering or enhancing their function. Since signaling

Drug development

Finding drug targets for cancer is not a simple matter. As Maria Dominguez (Institute for Neurosciences, Alicante, Spain) points out, “Now that we know the sequences of genes in the genome, we can attack every single one using RNAi reagents that we design from scratch.”

Although high-throughput RNAi can quickly uncover pathways components, their function(s) in living animals requires further investigation. So the CancerPathways team is generating transgenic fly strains each capable of expressing double-stranded RNA designed to knock down one gene in the genome. This library of transgenic RNAi fly lines allows scientists to study the function of genes in living tissues.

“CANCER IS EXTREMELY COMPLEX. IT IS NOT ONE DISEASE, BUT MANY DIFFERENT MANIFESTATIONS OF A SIMILAR PROBLEM.”

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but a suitable model for screening the effects of drug candidates on entire signaling networks within the context of cells in vivo.

Technology to therapeutics

“In terms of technology,” explains Michael Boutros, “in the next five years we will refine the tools for RNAi.” Beyond identifying cancer-risk genes, RNAi technology has potential therapeutic applications, too. “People are very excited about that, but we have to be cautious. The principle is very simple really; RNAi could be used to switch off genes that promote cancer in cancer cells. However, there are huge problems with implementing this technology.”

“Trials are currently ongoing on macular degeneration, for example, where it’s clear which genes are involved. RNAi probes for these genes are directly injected or applied topically. We’re at a much earlier stage with cancer. Everyone’s waiting to see what happens so we can construct a model of how RNAi drugs might be developed. We need proof of principle first,” confirms Michael.

For RNAi to be used as a therapy on human patients, many years of testing will be required. Like any drug it can have harmful side effects. Currently, the use of RNAi is restricted to cells grown in culture in the lab or in simple model systems like fruit flies. "There are not yet RNAi-based treatments for humans," explains Barry Thompson, "although one day there will be, and the public needs to learn about this technology sooner rather than later."
MEET THE SCIENTISTS

Michael is pioneering tools to explore gene networks that make proteins involved in signaling pathways in fruit flies. Flies have thousands of genes in common with humans. Signaling pathways exist in all animals from worms to humans where they orchestrate the finely tuned process of biological development from fertilized egg cell to adult. Many such pathways are implicated in human disease so understanding how they work in flies is of potential medical benefit.

Michael’s team has been working on the development of novel high-throughput screening platforms to rapidly identify genes by genome-wide RNAi approaches. Newly identified genes are being characterized using molecular and biochemical approaches in human cells and in Drosophila in vivo. Such a comparative functional genomics approach has led to the discovery of several new signaling components that are important in cancer. These include members of the Wnt signaling pathway, which is implicated in colon cancer.

The Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ) where Michael’s research team is based employs more than thousand scientists in the study of cancer research. The Institute is largely funded by the German Federal Government and their total annual budget is around 150 million Euros. The Institute aims to uncover fundamental processes in cancer and to develop innovative methods for diagnosis and treatment. There are seven main research areas: cell biology and tumour biology, structural and functional genomics, cancer risk factors and prevention, tumour immunology, imaging and radiooncology, infection and cancer, translational cancer research.

Michael Boutros

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Barry and Krystyna are at the forefront of technological advance in the world of fly biology. They are fascinated by the way that brain activity translates into animal behaviour. To address the question of how animals decide what to do, their research team studies the sex lives of fruit flies. Although their primary research interests are not directly related to cancer, the discoveries they have made about development translate into a better understanding of processes fundamental to cancer. In addition, they’ve pioneered the development of a massive library of transgenic fly strains, in excess of 22,000. Each one has a built-in RNAi construct designed to silence a specific gene. The effects of silencing genes can thus be studied in living animals. The library is currently managed by the Vienna Drosophila RNAi Center (VDRC), which Krystyna now heads.

There are almost 200 scientists working at the Institute of Molecular Pathology in Vienna. Their research covers a many life-science topics including computational biology, structural biology, biochemistry, cell biology, developmental biology, immunology, oncology, and neuroscience. The Institute is principally funded by Boehringer Ingelheim GmbH, but conducts independent, curiosity-driven research in the basic biomedical sciences. State-of-the-art facilities allow researchers to do proteomics, advanced light and electron microscopy, bioinformatics, histology, DNA-sequencing, peptide synthesis, and animal husbandry.
Martin and his research group are exploring the key players in a signaling pathway that derives its name from the Greek god Janus. The two-faced god of beginnings and endings is apt symbolic representation for its molecular namesake, the Janus kinase (JAK), whose two elements facilitate the dialogue between molecules outside of the cell and the genome within the cell nucleus.

The so-called JAK/STAT signaling pathway plays a role in blood development, cell division and the immune response in most organisms. The pathway is much simpler in flies than humans, but they’re essentially very similar. A molecule outside the cell, for example interferon, binds to a receptor on the cell-surface. JAKs inside the cell then bind to the receptor and are activated. They transmit their activity to molecules called STATs which are then transported into the cell nucleus, bind to DNA and prompt specific genes to start making protein.

Martin’s research is relevant to blood cell cancers that result from overproduction of abnormal blood cells in the bone marrow. Many such disorders have recently been attributed to a mutation in human JAK2. His team has shown that mutating JAK in flies hugely increases the number of blood cells and growth of tumours, but that mutating other JAK/STAT pathway components in addition can ameliorate disease progression.

The MRC Centre for Developmental and Biomedical Genetics (CDBG) is located within the Department of Biomedical Science and has a central purpose to bring together developmental geneticists with clinician scientists. With sixteen full members and eight associate members, each heading an independent research laboratory, the CDBG has around 100 post-doctoral research assistants, post graduate students and technical staff and attracts annual grant income in excess of 2 million Euros. The University of Sheffield itself is committed to enhancing the European dimension of its work and participates in over 50 Framework projects with a total budget of 30 million Euros.

**Martin Zeidler**

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Maria studies processes fundamental to biological development, which are also relevant to cancer. Signaling pathways that govern the sophisticated orchestration of cells during embryonic growth are implicated in many kinds of cancer. Her team uses the fruit fly, *Drosophila melanogaster*, to figure out how signaling pathways function in eye and blood development. Such pathways are very similar in all organisms so fly research teaches us a lot about humans.

The group is interested in the role of a signaling pathway called *Notch* in human disease. The activity levels of this pathway vary in different body tissues. It has often been observed that *Notch* is overactive in cancers, although this is not true for all cancers. In contrast, *Notch* is underactive in neurodegenerative diseases like Alzheimer’s. So understanding how the pathway is controlled may lead to new therapeutic approaches.

The Instituto de Neurociencias de Alicante (INA) is a joint research unit (JRU) of the University Miguel Hernández de Elche (UMH) and the Spanish National Research Council (CSIC). The Institute has around 50 researchers employed in the field of neurosciences. The INA is part of European Neuroscience Institutes (ENI)-NET, a network of European research institutions in the field of neurosciences committed to the promotion of scientific excellence across Europe.
Wolfgang leads a computational biology research group in the European Molecular Biology Laboratory (EMBL). He has appointments at the Genome Biology Unit in Heidelberg and at the European Bioinformatics Institute (EBI), one of the world’s largest bioinformatics service providers, in Cambridge. His group studies genotypes and phenotypes on a genome-wide scale: how do variations in the genomes of individuals shape their complex phenotypes? To this end, they develop computational methods in statistics, signal and image processing.

They work together with experimental laboratories in systems genetics and functional genomics to develop the best methods for designing and analysing genome-wide experiments whose aim is to unravel the mechanisms of genetic inheritance, gene expression, signal transduction and how they shape phenotype. Most phenotypes, including human diseases, are complex: they are governed by large sets of genes and regulatory elements. Wolfgang’s aim is to map these complex networks and eventually, to devise strategies for designing phenotypes by engineering combinatorial perturbations.

Wolfgang’s research is driven by new technologies, and he employs data from high-throughput sequencing (ChIP-Seq, RNA-Seq), tiling microarrays, large scale cell based assays, automated microscopy, as well as the most advanced methods of computational statistics. He is a core member of the Bioconductor project, a leading platform for the development and publication of software for functional genomics data analysis and modelling.
Barry’s research focuses on a signaling pathway known as Hippo. Defective components in the pathway cause the formation of large tumours in flies. Together with his research team he has developed techniques to study the Hippo and other pathways in living animals. Using RNAi technology Barry’s team can turn down the activity of genes that make the Hippo pathways components to investigate their effects on development.

The Cancer Research UK London Research Institute (CRUK-LRI) aims to improve our understanding of cancer. Across some 50 CRUK laboratories, researchers study the biology of tissues and organs, molecular cell biology, the cell cycle, as well as chromosome and DNA repair. Barry was recently recruited to study cancer biology using the fruit fly Drosophila as a model system.

Barry’s team: the Epithelial Biology Laboratory is now working in collaboration with the Vienna Drosophila RNAi Screening Centre (VDRC), headed by Krystyna Kelemen, and with Barry Dickson’s lab to conduct an in vivo genome-wide RNAi screen to identify novel molecular regulators of cancer-relevant processes in the fly.
Buzz and his research team are exploring how changes in cell shape and dynamics can contribute to cancer. Together with other members of the CancerPathways research network he has helped pioneer new large-scale GM technologies such as RNAi in flies to hunt for cancer-risk genes. This is key to uncovering new therapeutic targets and improving our understanding of how cancer develops.

His team has created a database called FLIGHT to facilitate the analysis, integration and dissemination of data from RNAi screens. The lab was recently awarded two major cancer grants from the Association of International Cancer Research and Cancer Research UK to use RNAi to search for new cancer-relevant genes that play a role in the formation of the cytoskeleton.

University College London (UCL) is one of the largest universities in the UK. With 27,000 staff and students and 19 Nobel prizes under its belt, the University is widely recognized for excellence in teaching and research. The UCL’s Laboratory for Molecular Cell Biology (LMCB) constitutes the primary Medical Research Council (MRC) funded cell biology institute in the UK. Together with the MRC Cell Biology Unit (CBU) some 130 scientists carry out research relevant to many human diseases including cancer.
József is interested in the genes that help a cell to orient itself within a tissue. His research team is on the hunt to identify the key players in cell polarity. The same sets of genes control polarity, not only within different fly tissues: wing, eye and thorax, but in different animals. For this reason flies are fundamental to understanding how healthy tissue forms, which is critical to improving our understanding of what goes wrong in cancer, where polarity is often lost.

The Biological Research Center at Szeged is the largest molecular biology institute in Hungary. In 2000 the BRC was nominated as a Center of Excellence by the European Union. The 300 scientists who work there also participate in educating students in addition to running international training courses for neighbouring and developing countries.

The institute has been recognised for its contribution to the development of important resources to study the fruitfly, *Drosophila*. József and his group are at the core of such work on development. They have developed new genetic techniques for studying flies and are experienced in the testing of new pharmacological compounds, having worked with Aventis CropScience (now belonging to the Bayer Group) and SOLVO Biotechnology Ltd. (Szeged) to develop simple drug tests using flies.

**József Mihály**

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[www.szbk.u-szeged.hu](http://www.szbk.u-szeged.hu)
### GLOSSARY

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>amyloid plaque</td>
<td>Protein deposits that accumulate in the brain of Alzheimer’s patients</td>
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<tr>
<td>assay</td>
<td>A test or measure of the activity of a drug or biochemical in an organism or organic sample</td>
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<tr>
<td>cell cycle</td>
<td>The series of events that occur in a cell before it reproduces itself</td>
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<tr>
<td>chromosome</td>
<td>An organised structure of DNA and protein found in cells. DNA – containing many genes, regulatory elements and other nucleotide sequences – is coiled around histone proteins. This is divided into discrete units (23 pairs in humans) called chromosomes</td>
</tr>
<tr>
<td>DNA (deoxyribonucleic acid)</td>
<td>A nucleic acid containing the genetic instructions used in the development and functioning of all known living organisms and some viruses</td>
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<tr>
<td>Drosophila melanogaster</td>
<td>A two-winged fly, commonly known as the fruit or vinegar fly, which is one of the most widely used model organisms for biological research</td>
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<tr>
<td>gene</td>
<td>A segment of nucleic acid that specifies a trait</td>
</tr>
<tr>
<td>genome</td>
<td>The entirety of hereditary information, which varies between species, encoded in DNA</td>
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<tr>
<td>GSI (gamma-secretase inhibitor)</td>
<td>A substance that inhibits the actions of gamma-secretase enzymes, which are involved in the formation of amyloid plaques</td>
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microarray
A collection of probes spotted on a solid surface, such as glass and plastic. Probes may be DNA or protein fragments or chemical compounds. They are routinely used to search for proteins that bind to them providing a multiplex way to perform large-scale screens.

RISC
(RNA-induced silencing complex)
A multiprotein complex that incorporates one strand of a small interfering RNA (siRNA), which acts as a template to recognize complementary mRNA and destroy it. This is part of gene regulation by microRNAs but also in defense against viral infections, which often use double-stranded RNA as an infectious vector.

RNA
A nucleic acid, similar to DNA, made up from units containing a sugar, phosphate and nitrogenous base. RNA uses the sugar ribose and the base uracil, whereas DNA is composed of deoxyribose and thymine in place of uracil. RNA has many functions in the cell including the processing of genetic information into protein.

siRNAs
small-interfering RNAs form a class of double-stranded RNA molecules, 20-25 nucleotides long, that are most notably involved in the RNA interference (RNAi) pathway, where they interfere with the expression of a specific gene.

tumour suppressor
A gene or its protein product, which protects a cell from cancer. Mutations to the gene cause a loss or reduction in the protein function and the cell can progress to cancer.
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