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Twitter, Facebook and Co...

...have become indispensable in many people’s lives. Often, even before these people get up in the morning, they check their feeds for the latest news, conversations and funny cat pictures. The science community has also taken advantage of the fast information flow – in the hope of spreading news from the labs more widely, reaching more people and perhaps even starting one or the other constructive discussion.

Social media has even found its way into new evaluation methods of research importance. “Knowing who’s talking about your research and what they’re saying” advertises, for instance, altmetrics. Similarly, PLoS’ Article-Level Metrics (ALM) incorporate blogs, tweets and Facebook mentions, to “document the many ways in which both scientists and the general public engage with published research”.

But does a tweet about a scientific publication really reach more people? Make more people interested in science? Attract a greater deal of attention? Does it fulfil its promise?

In a new paper in PLoS ONE, scientists from Spain, The Netherlands and the US analysed the role Twitter plays in scholarly communication (PLoS ONE, 12(8): e0183551). Their paper’s title, “The unbearable emptiness of tweeting – about journal articles”, already suggests that perhaps the metric is not as meaningful as many think (hope) it is.

The authors, analysing tweets about dentistry papers, first set the scene. “Proponents described largely idyllic scenarios emphasising Twitter’s potential for aiding career development, connecting with colleagues, building relationships with patients, enabling virtual journal clubs and scientific conferences, complementing traditional teaching methods, critically appraising and reviewing research, or all of the above.”

In an ideal world, science and society would clearly benefit from this way of knowledge propagation. But, in the real world, the authors saw “much presumably human tweeting almost entirely mechanical and devoid of original thought, no evidence of conversation, tweets generated by monomania, duplicate tweeting from many accounts under centralised professional management and tweets generated by bots”. All these tweets surely won’t attract any extra attention.

Less than 10% of tweets gave the impression that the Tweeters actually read the paper and were genuinely excited about it. “Such accounts have modest metrics – numbers of tweets, followers, friends,” the authors point out.

To see how much truth there is in this study, we drew our own random sample – tweets about the latest paper by Melina Schuh and Binyam Mogessie titled “Actin protects mammalian eggs against chromosome segregation errors” (Science, 357(6353):eaal1647). As a matter of fact, it doesn’t paint a simi-}

literally bleak picture. At the time of writing, the paper had gathered 66 tweets from 65 users. About half of those tweets indeed were machine-like retweets but the other half were very personal, encouraging people to check out the paper themselves. “Super cool story............a must read!”, “Wow. You think you understand the basics of a thing in biology, and then someone discovers something unexpected” and “Yet another one of my many dogmas bites the dust! Science can be so cool sometimes” were just some of the comments accompanying a direct link to the paper.

But that’s just one little example. “Tweeting is an activity created by a company whose value derives from growth in that activity. The platform is designed to lower barriers to tweeting because the easier it is to tweet, the higher the tweet count and so the higher is the company’s value,” the PLoS ONE authors write. “These design features encourage quick, non-human-like action that generates tweets that increase measures of engagement with the platform just as much as a unique, thoughtful, funny piece of text. (…) In the context of tweeting about journal articles, enrolling people in an algorithmic exercise to maximise tweet counts contrasts with the deeply human activity of advancing knowledge,” the authors find and add “Twitter’s immediacy and speed are mismatched to the slow pace of knowledge advance. It’s thinned out, 140 character missives contrast with the thick and rich texts of research and scholarship. Twitter’s valuing of volume contrasts with the thoughtfulness of high quality scholarship.”

Strong words but is the judgement too harsh? “In my view their critique of Twitter discourse is misplaced, because Twitter is not supposed to be a replacement for ‘high quality scholarship’ but is rather a medium of conversation,” Neuroskeptic points out in his blog. “One could take Robinson-Garcia et al.’s points and apply them equally well to the conversational medium of human speech. In fact, if you recorded the spoken words of all the attendees at a scientific conference (say), you would probably conclude that science was doomed.”

Perhaps we can agree that social media shouldn’t be taken too seriously. It’s just an additional tool to spread and discover un-bearably fascinating scientific news.
Soon, you won’t even have to leave your home to attend an academic conference. Online scientific conferences are becoming more and more popular (p. 16).

Mating season is tough for northern elephant seals. Isabelle Charrier discovered that males are able to recognise and remember their rivals’ vocalisations to avoid fights (p. 32).

Synthon, a midsize company from Nijmegen, Holland, has trouble with all-powerful generics producer, Teva Pharmaceuticals from Israel. It’s about patents (p. 43).

Correlative light and electron microscopy (CLEM) combines the best of both worlds to get a clearer picture of cells’ ultrastructures (p. 54).
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How many animals do you see? Two? If you look closely, you can see a third creature in this photo, which was named runner-up in this year’s BMC Ecology Image Competition. Blending in nicely with the white flower in the background is a crab spider, feasting on the bee. According to one of the competition’s judges, the true star of the image is, however, the smaller parasitic fly, which is also attacking the poor bee. “This parasite, tack sharp, commands the attention it deserves as a major player in this interaction and in ecosystems in general,” he said. The photo titled “Connections” was taken by Roberto García-Roa of the University of Valencia, Spain. “Conservation cannot be understood without taking into account the interaction among species,” García-Roa wrote in the image caption. “The disappearance of one species might provoke that other connected species (prey, predators, etc.) can suffer direct consequences.” Now in its fifth year, the BMC Ecology Image Competition has again received entries by talented shutterbug-ecologists from across the world, showcasing research that is increasing our understanding of ecosystems worldwide and the beauty and diversity of life on our planet.”

-KG-

PAUL THE POSTDOC

BY RAFAEL FLÓREZ

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Recently Awarded

The Albert and Mary Lasker Foundation honoured three scientists with its eponymous awards and a cheque for $250,000 (ca €220,000). Michael N. Hall from the University of Basle won the Lasker Award for Basic Medical Research. Back in the 1980s, Hall studied the actions of the anti-fungal agent rapamycin in Saccharomyces cerevisiae. By trying to identify proteins that interact with rapamycin, he discovered two proteins, Target Of Rapamycin (TOR) 1 and 2. These two proteins turned out to have an important physiological function, not only in yeast but in mammals, too. They regulate cell growth, dependent on nutrient availability. When the TOR system is disrupted, diseases, such as diabetes or cancer, can be the consequence. The Lasker Foundation’s Clinical Research award is shared by Douglas Lowy and John Schiller of the US-based National Cancer Institute. The duo developed vaccines against the human papillomavirus, HPV, causing cervical cancer.

One half, i.e. 375,000 Swiss Francs (ca €310,000) for research projects, the other half for themselves; the International Balzan Foundation recently awarded one of their Balzan Prizes – in the category Immunological Approaches in Cancer Therapy – to James Allison from the University of Texas, Austin, and Robert Schreiber, based at the Washington University School of Medicine, Saint Louis. Schreiber discovered that the immune system plays an important role in cancer pathogenesis. His experiments showed that tumours can fool the immune system and escape detection. Allison, in turn, studied how the immune system can be guided back to the right track. He developed a monoclonal antibody, which blocks the T-cell inhibitory molecule, CTLA-4. This checkpoint blockade antibody (ipilimumab) has been in clinical use for the treatment of melanoma. One of the annually alternating categories for next year’s Balzan Prizes will be Chemical Ecology.

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Wasp project annoys environmentalists

Beer Traps

Involving the public in authentic research projects is a good way to better connect science with society. In late August, entomologists from the University College London launched another such citizen science project – the Big Wasp Survey. “We know bees are struggling but what about wasps?,” the scientists wondered and initiated the survey; the first of its kind in the UK.

“This is about raising public awareness of these much-maligned insects. They are the gangsters of the natural world, the top predators, without which we would be inundated with aphids. They pollinate, they disperse seeds. They are on a par with bees with the ecosystem services they provide.” of the project leaders, Seirian Sumner, told the Guardian.

Therefore, it’s important to learn as much as possible about these little “picnic ruiners”. For instance, the scientists hope to find out, which species live where, what factors are affecting wasp populations and how colour patterning within species varies across the country.

To do so, Sumner and co. asked people across the UK to set traps in their back garden – beer traps, to be exact – because that’s what wasps like best. After a week, beer-drenched wasps should be sent to the scientists for identification and counting.

Although this method of collecting research subjects sounds a bit weird, it’s common amongst bee-keepers to lure away wasps from their bee hives. Beer traps are also commercially available for public open spaces and entertainment parks. “While we are asking people to kill some wasps, which is a bit unusual for a project aimed at conserving them, it really is the only way that we can identify the wasp species around and be sure that the information we get from the project is worthwhile. At this time of the year, wasp colonies are at the end of their life and the wasps we catch are old workers, who will die soon anyway. This means our methods won’t have any significant effects on the overall populations,” the scientists assure.

A project like this is also sure to bring some environmentalists on the scene. “We are very uncomfortable about a project that is harnessing the UK public’s hatred of wasps and encouraging them to kill wasps wholesale. These traps are indiscriminate and will attract and kill lots of insects, including flies and bees. It is not clear that the scientific aims add sufficient value to justify the slaughter – the ends do not appear to justify the means,” Matt Shardlow, CEO of insect conservation charity Buglife counters.

“We’ve thought very carefully about this. We are experts in wasp ecology and life history, unlike Buglife. (…) These traps are the standard method to monitor wasp populations around the world. Sometimes you get flies in them, sometimes you get the accidental falling of an insect in them but there’s no way a beetle or bee would be attracted to them,” Sumner said.

Database must rename disease

It’s All in the Name

There are many reasons to request the retraction of a published paper. Here’s a new one (first reported by Retraction Watch).

In The Netherlands, a man has a son with a rare disorder: short stature, long eyelashes, bushy or arched eyebrows, low back hairline, low nasal bridge, low-set and deformed ears, short fingers and abnormal nails. Keen to find out the underlying genetic cause, he asked scientists, among others at the Academic Medical Center in Amsterdam, to analyse his son’s DNA. Indeed, they are successful and find missense mutations in the RPS23 gene, coding for ribosomal protein, uS12. “The amino acid substitutions lie in two highly conserved loop regions of uS12 with known roles in maintaining the accuracy of mRNA codon translation. (…) uS12 variants impaired the accuracy of mRNA translation and rendered cells highly sensitive to oxidative stress,” the scientists wrote in their American Journal of Human Genetics (AJHG) publication (100(3):506-22).

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The researchers’ findings have also been added to the Online Mendelian Inheritance in Man (OMIM) database, “a comprehensive, authoritative compendium of human genes and genetic phenotypes”. But the disease needed a proper name. “Sometimes something has too many features to be described succinctly. In that case, the default way to name something is to use the first author’s last name and last author’s last name,” OMIM director, Ada Hamosh, told Retraction Watch. In this case, there were just too many first co-authors, so OMIM settled on the study’s last author’s name and called it the MacInnes Syndrome.

But the father was not happy about it. Mainly, the term “syndrome” bothered him. “Syndrome is a disease,” he told Retraction Watch. In the hope that if the paper is retracted, the disorder’s name would disappear, too, he withdrew his father’s consent to participate in the study and contacted AJHG. For the journal’s editor, David Nelson, however, this is not a sufficiently strong reason to retract the entire paper. “Published scientific articles deriving from the studies are not subject to the consent withdrawal and this was confirmed by individuals familiar with European Union Regulations relating to personal data,” he told Retraction Watch.

Still, the father got what he wanted, to some extent. His son’s condition is now listed on the OMIM database under the name “Brachycephaly, Trichomegaly, and Developmental Delay” or BTDD. MacInnes Syndrome, however, remains as an alternative name.

**X-ray laser launch**

**Hamburg High Tech**

Fast, faster, XFEL. In September, the world’s largest X-ray laser – the European X-ray Free Electron Laser – together with its superfast detector, has been put into operation. Similar to CERN in Switzerland, the European XFEL accelerates particles, in their case electrons, to high energies and then forces them to follow a zigzag course through a magnetic tunnel. This way, the electrons emit X-ray radiation, which increases along the way and “produces extremely short and intense X-ray flashes with the properties of laser light”.

Construction for this 3.4 km-long facility (including a 2.1 km long accelerator tunnel) began in early 2009 and cost €1.22 billion. It runs from DESY (German Electron Synchrotron) in Hamburg to the 20,000-resident town of Schenefeld. The annual budget is €17 million.

The recently installed Large Pixel Detector records an unimaginable 4.5 million pictures per second and has a very high dynamic range. It’s able to pick up both single photons and a bundle of several thousand photons in two neighbouring pixels. “We now have one of the ‘eyes’ for our instrument. We are proud to have received the fastest X-ray detector on this planet!” XFEL lead scientist, Christian Bressler, proudly stated in a press release.

What can you now do with the record-breaking instrument? Because it is so fast, researchers will be able to follow and film chemical reactions that happen in the blink of an eye, such as the conversion of light into chemical energy in plants or the actions of catalysts. “Since the duration of the flashes is less than 0.1 trillionth of a second, snapshots can be taken without moving details becoming blurred. Thanks to the short wavelengths, even atomic details become visible,” the website explains.

In a second experimental setup – the SPB/SFX (Single Particles, Clusters and Biomolecules/Serial Femtosecond Crystallography) instrument will help scientists elucidate the 3D structure of proteins or even entire viruses. “Its X-ray flashes are so intense that scientists can also use small crystals of bad quality or even do away with crystallisation altogether. In addition, the duration of the flashes is so short that the molecule hardly changes during the exposure. The molecule starts to decay – due to the enormous forces generated by the strong incident light – only after the X-ray flash has passed the sample and the picture of the atomic structure has been taken.”

Access to the facility is through a proposal-based selection procedure. The first 14 research groups have already been invited and welcomed.

**Manuscripts from dishonest researchers Just Like Any Other**

Regular followers of the Retraction Watch blog have certainly noticed that hardly a day goes by without the news of a newly retracted study. Many of these publications involve researchers, who took a shortcut to success and manipulated their data. Some of those researchers go into hiding after their misdeeds have been revealed; others accept having made a mistake and continue their research.

Just like Olivier Voinnet and his frequent co-author Patrice Dunoyer. After eight retractions and numerous corrections and errata, Voinnet published four new papers in 2017. The last one in Genome Research. Despite a temporary suspension from the French National Centre for Scientific Research (CNRS), also Dunoyer has kept busy, publishing three new papers this year, amongst others in Nature Plants.

This raises the question, how editors should handle manuscripts from researchers found guilty of misconduct – eye them even more carefully or perhaps reject them altogether? Nature Plants editor, Chris Surridge, wrote in an accompanying editorial, “Sport has a long and inglorious history of athletes using unethical means to defeat their competitors. (...) In science, the equivalent to doping is data manipulation. Tweaking a blot or ‘tidying up’ a micrograph to better support a study’s conclusions can be thought of as similar to taking a banned steroid in training.” About Dunoyer’s manuscript submission, Surridge revealed that they treated the study just like any other manuscript. It went through two rounds of review, passing eight reviewer eyes.

“It is not our role to investigate scientific misconduct or determine appropriate sanctions,” Surridge told The Scientist. “Our role is to ensure that the studies that are submitted to us and which are ultimately published are as accurate and reliable as possible, irrespective of whom the authors are.”

Committee on Publication Ethics secretary Charon Pierson agrees that journal editors’ only responsibility is to check manuscripts for their accuracy. “To deal with the scientists themselves – that’s the realm of the institutions, the laboratories, the funding agencies, the governments, all of those pieces of the puzzle,” she told The Scientist.

“As far as I am aware, there hasn’t been very much response from the community at least not much has reached me. There was a small flurry of activity on social media at the end of July and I’m not at all...”
# EMBL 2018

## Conferences

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surprised that some people had strong reactions. On the other hand, the feedback that I have received directly has been generally supportive of our position,” Surridge tells Retraction Watch.

So, scientific life moves on for Dunoyer and Voinnet but, as it appears, some inconsistencies remain. In a PubMed comment about Dunoyer’s Nature Plants paper, Morten Oksvold, cancer researcher at Oslo University Hospital, criticises that the paper cites a publication, which is very likely to be retracted soon. “I find it problematic that Nature Plants accepts this kind of practice, by apparently legitimating well-documented, intentional manipulations as facts.”

Medico-historical stamps

Post from the Past

To celebrate its 20th anniversary, Karolinska Institutet’s (KI) Hagaström Library recently collaborated with the Swedish post for a new stamp series. The library houses KI’s valuable collection of old and rare books from the 15th to the 19th century, including works from Charles Darwin (“The Expression of the Emotions in Man and Animals”), Alexander Fleming (“On the Antibacterial Action of Cultures of Penicillium”) and, of course, Carl Linnaeus (“Materia Medica”).

From that collection of more than 40,000 books and manuscripts, three illustrations of medical plants have been chosen for the stamp series. “Medicinal plants, spices and herbs were considered vital. They were used for the stamp series. “Medicinal plants, spices and herbs were considered vital. They were considered effective medicines,” Hjalmar Fors, librarian at the library said during a press conference.

The stamps have a value of 21 krona and depict a broadleaf plantain (Plantago major), St. John’s Wort (Hypericum perforatum) and the common foxglove (Digitalis purpurea).

The broadleaf plantain comes from the “New Kreüterbuch”, published in 1543 by German physician and botanist, Leonhart Fuchs. By the way, the botanist’s name lives on in the Fuchsia plants.

The drawing of the Hypericum by Johan Wilhelm Palmstruch stems from the book Svensk Botanik from 1803. “Palmstruch was a skilled draughtsman, who, in collaboration with the engraver Carl Venus, started to illustrate Swedish plants, which became the first illustrated Swedish flora,” the library informs.

Lastly, the Digitalis purpurea was taken from the 18th century book “Botanica Pharmaceutica” by Andreas Friedrich Happe. “The book is very rare,” Gertie Johansson from Hagaström Library tells Lab Times. “It was published at the author’s own expense, probably only for the 71 subscribers. Happe had studied pharmacy in Berlin and made drawings for the Society of Sciences in Berlin. He also published some works about mushrooms, lichen, insects and butterflies.”

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Birds of a Feather

Spanish scientists eyeball the plumage patterns of thousands of birds.

Painters, just like van Gogh or Monet, created their amazing masterpieces with – at least – two types of brushes: broader ones for the colours and smaller brushes for detail and shading. Birds, basically, do the same. They, however, do not use brushes and different hues of acrylics or water colours; they use pigments, such as melanin, carotenoids and, in rare cases, psittacofulvins and turacin. “The combination of different colours within or between feathers produces complex pigmentation patterns that are also extraordinarily diverse even if the pigment palette is very restricted,” write Ismael Galván and colleagues from CSIC in Sevilla (Physiol Biochem Zool, 90 (5), 600-4).

These pigmentation patterns come in different shapes and range from mottles, to scales and bars to spots – just think of a peacock’s tail feathers. The Spanish scientists now wondered how these complex patterns are produced – through interplay of all pigments? Interestingly, only melanin production is under direct cellular control, being endogenously synthesised in melanocytes. Carotenoids, in contrast, are taken up in food.

Examining more than 9,000 extant birds in the “Handbook of the Birds of the World”, the authors noticed that a majority of complex pigmentation patterns are made up of different variations of black, gray, brown and orange – hues, hinting at the involvement of melamins, such as eumelanin and pheomelanin. Only 53 bird species – out of 2,918 exhibiting complex patterns – used other pigments than melanin. Among them the rose-crowned fruit dove (Ptilinopus regina), the orange-breasted fruiteater (Pipreola jucunda) and the yellow-billed stork (Mycteria ibis), whose scarlet wing feathers are most likely produced by carotenoids. “It is likely that the few exceptions of complex plumage patterns with no contribution of melanin-based colours are due to exceptional innovations in the metabolism of carotenoids,” the authors assume.

Melanin-based or not, evolutionarily speaking, there must be a reason why birds invest so much in creating these complex patterns. And it doesn’t necessarily have to do with staying out of sight and camouflage. “Alternatively, complex plumage patterns may convey information about individual attributes and have a role as sexual signals,” the bird experts conclude.

(More research results from European labs on pp. 28-33)
Macho Science

It's no fun getting old, I can tell you. Every night my bones and muscles protest loudly just at me spreading my wings. Moreover, wind and weather feels chillier than ever lately; at least my beak keeps dripping most of the time.

Much worse, though, all those yummy little furballs appear to be whizzing over the forest ground faster than ever before. Often too fast for me, so that most nights only “the old and sick” remain an easy target for my dinner. Brrr!

And then there are certainly all those beautiful and elegant lady owls, who nowadays don’t even spare me the slightest glance as they fly by. Damn hormones! Still floating around in my body but only serving to shatter my ego into ever smaller pieces...

Enough whining! There is at least one thing that I definitely do not miss at all from my younger days: brood care. Our damned hormones drive us to mate and then relentlessly force us into the whole programme: the lady lays the eggs and incubates them until the babies hatch, at the same time the guy has to hunt and deliver the food – first for the breeding lady alone and, after hatching, over weeks and weeks for the fledglings as well. Believe me, in my better years I hunted more than two thousand mice to feed my whole, actual family through such a reproductive cycle – which makes twenty to thirty per night...

Hah, I hear you humans spouting off about how to balance working in science and raising a family. But what should we birds say? You definitely cannot begin to imagine how much the way we reproduce distracts us from doing science. We have absolutely no choice in the matter! Hormones, old chap, hormones…

Well… I haven’t started telling you this, just for the sake of a good old peck at you humans (although, there’s nothing I enjoy more, as you know!). You see, the sad fact is that even a few of our bird fellows obviously don’t have a clue as to exactly how strong these reproductive forces are for the vast majority of us! And that it is not a point of not wanting to escape them – but that we simply cannot! Neither females nor males!

What kind of nasty consequences can arise from such incredible ignorance is perhaps best exemplified by the story of Bowerbird. Allow me to enlighten you...

Bowerbird was a strange guy, who showed up in our forest one day out of the blue. It turned out that he had acquired a grant from the Bird-of-Passage Programme, which aimed at luring eminent bird researchers from all parts of the globe to our forest, in order to lead a group on a specific project for a given time.

To put it bluntly, I didn’t like Bowerbird from the first moment I saw him perched on one of the highest branches, staring arrogantly around with his pungent blue eyes. It was my old chap Skylark who finally told me a bit more about Bowerbird’s species. In actual fact, he had once spent a sabbatical in their homeland and so he knew a lot about bowerbirds, first hand. I liked almost nothing of what he reported; however, the most important information relevant to our story was as follows: Their hormones drive the male bowerbirds to build up elaborate bowers, which in some what crazy effort, they decorate with lots of colourful stuff, to attract females for mating. Well, what shall I say… Everybirdy to his own! What Skylark told me next really took the biscuit, “A successful male who has built a good bower might attract more than 25 females and mate with all of them over one mating period. Other countries, other habits – shall we say!” Enough said!

I let that sit for a while and finally pondered aloud, “But that means that in the end the females…”

“Exactly!” Skylark nodded. “They are left completely alone with breeding the eggs and raising the fledglings. Their males do not take any part in parental care. They just donate their sperm and send them on their way. Real macho birds!”

Given this, it was rather foreseeable what finally happened… Bowerbird’s first victims were a pair of crested grebe PhD students. Unfortunately, he had obviously not known before that grebes are among the birds with the longest breeding times of all – and, furthermore, that both breed: male and female. When they finally returned in late October, after four months of breeding absence, they found their benches occupied by two starlings – genuine short-breeders (for those of you not in the know).

Even worse was what happened to Bowerbird’s first postdoc, a white stork lady. Again, Bowerbird had only been impressed by her elegant appearance and had not been aware of the rather long breeding and raising time that white storks generally have to invest in their reproductive success. When the lady was about to lay her second set of eggs, Bowerbird fired her without further ado. He didn’t care much of a feather that in doing so, he killed off her whole scientific career before it had really taken off.

If that wasn’t enough, Bowerbird’s egocentric recklessness didn’t end there. He took all the clones and cell lines the white stork lady had produced during her postdoc time and threw them away. He did, however, keep her lab book; he gave it to his technician, also a young bowerbird from his homeland, and instructed him to repeat all the experiments, exactly as noted therein. Within a short time, he had reproduced all the results of White Stork – and Bowerbird could finally publish the corresponding article, without her name, in one of our very top journals, Bird Genetics...

My dear readers, I’ve never cared much about things like Gender Mainstreaming (and its sometimes all-too crazy excesses) but old owl that I am now, it is still one of my most pleasurable memories to recall how, after two or three more similar incidences, our acting Women’s Officer finally chased that dastardly Bowerbird far out of the forest and into pastures unknown. She was an eagle lady with a recalcitrantly strong beak and particularly sharp talons…

Comments: owl@labtimes.org
Fake or Real?
By our corresponding author, Justin Blink

Manipulating digitalised photographic images is easy. Their increasing prevalence in published scientific articles has become a source of concern. But it’s not just scientists, who have an image problem; it seems humans as a whole are pretty poor judges of image manipulation, even when they’re told the images are altered.

In her recent study, “Can people identify original and manipulated photos of real-world scenes?”, Warwick University’s Sophie Nightingale claims to have shown for the first time that people’s ability to detect manipulated photos of real-world scenes is “extremely limited” (Cogn Res Princ Implic, 2:30).

We are frequently exposed to manipulated images in our daily lives – for example, in advertisements, in the news, on social media – and images can have a powerful influence on the things that we remember along with the decisions that we make, says Nightingale. They can affect our perception of past events, current political debates and legal or scientific evidence.

Worried about people’s capacity to detect trickery with their own eyes, previous studies have used images of geometrical shapes to test our ability to visually detect distortions in shadows, reflections and perspective. This latest study now examines whether people are similarly poor at detecting inconsistencies within images of real-world scenes, featuring people, cars, houses, trees, etc.

Real world view

Nightingale prepared an internet test, in which hundreds of volunteers, recruited over the internet, looked at a series of ten photographs: five unmodified originals and five that had been altered, using the GNU Image Manipulation Program (GIMP). The latter displayed one of five different, commonly used manipulation techniques – airbrushing (e.g. removing facial spots, wrinkles or sweat), addition or subtraction of some feature, geometrical inconsistency (e.g. stretching an object), shadow inconsistency (e.g. pointing towards the sun) and super-additive (the previous four techniques combined).

At the start, participants were clearly told they were being tested for their ability to detect whether photographs had been digitally altered. They were expected to look carefully for signs that the photos had been modified. There was no time limit for their examination. Even if they did not think a photo had been altered, they were asked to predict on each photo where they thought a manipulation might be located.

Since her online test is still open, you can even evaluate your own ability to detect the manipulated photos and to locate any changes (https://tinyurl.com/y9x66uw). At the end of the test, you receive a score out of ten and are told, which were the originals and which the fakes.

Despite knowing in advance that they would see altered photos, participants did not do very well. They had a one in two chance (50%) of getting the right answer. In fact, they identified 58% of the unaltered images and 65% of the manipulated photographs, i.e. they missed a third of the fakes. On the photos, they correctly located 56% of the manipulations.

Nightingale claims that her research shows people are quite unlikely to distinguish between real and fake images in newspapers/magazines or on the internet. She suggests future research should train people to improve their ability to detect false images.

Inappropriate images in science

Obviously, science is one of the domains, in which the ‘truth’ of photographic images is vital. Last year, however, Retraction Watch reported, “One in 25 papers contains inappropriately duplicated images” (19/4/16). A visual study by Elizabeth Bik of 20,621 published papers found 782 instances of ‘inappropriate’ image duplication. Her initial screen involved directly looking at the images without software. She found it easier to spot problems in photographs of Western blots because every band has its own characteristics – “they’re like faces”. Some examples were so obviously copied it was “almost funny in a disturbing way”. Like Nightingale, Bik thinks people can be trained to see something wrong but admitted she had probably missed some forgeries. Her highest detection rate was 12.4% in the International Journal of Oncology.

Nightingale says, we are swamped with photos – on average, more than 350 million per day are uploaded to Facebook (over 4,000 photos per second!). And it appears, we are regularly exposed to a mix of real and fake images: a global survey of photojournalists found 51% often enhanced unprocessed files and 25% admitted to altering the content of photos.

Image forensics has been proposed as a solution but can we really test every photo? Moreover, even with software assistance, how can you detect an unmanipulated photograph that has been labelled as showing something completely different, e.g. a perfectly good experimental result for one protein fraudulently re-named to ‘show’ a result for a completely different protein? Detecting such fraudulent use of image labels extends beyond visual perception to the credibility of what is claimed in the accompanying text. Perhaps, as Retraction Watch notes, it is not so surprising that some authorities would prefer to look the other way.
Standing Still

Nero,

Apparentally, the greatest skill the former Ingerland international Teddy Sheringham possessed, was to stand still and look wise. As you may remember, the Ingerlish are renowned for their 100 mph fussball spieler. Teddy was different. He had a Yoda-like ability to project future play. His unmoving would predict when the ball would transit into his sphere of influence. Lucky for him, he possessed this skill, as his other defining feature was a complete lack of pace.

As a young buck, I offered the alternative side of this coin. I was recruited to a team of largely veteran footballers. They were all well over 45 – many even beyond a half-century and not out. They would amble into the dressing room; mummify their gnarled and varicose limbs with stretch bandages before entering the pitch. The game would then be played at their preferred pace, enforced by their excellent technical skills, deep footballing intelligence and a global wisdom that often transfixed opponents.

Directing the legs

These opponents were usually much younger but overly reliant on their physical attributes. The vets’ wisdom included a realisation that the team would achieve most success if supplemented with three or four young players. These would provide the “legs”, i.e. the ability to run! This allowed for a potent tactical mix of gegen and nicht-so-gegen pressing.

Indeed, the vets were particularly good at verbally directing where the young legs should run. They also realised that identifying a goalkeeper among the three or four youngsters was key. This meant they had someone, whose vision had sufficient transition between short and long distance, without the need for verifocal or distance and reading glass combo. This made the team much less susceptible to a lob from 40 yards. Indeed, armed with young legs and vision, these veteran boys remained serial cup winners well into their 50s. I certainly never played a better standard of football.

Pipetting in the fading light

As I informed you, I have recently re-entered the field of play and subjected the world to a sustained period of pipetting. This has seen me shuffle along the bench, adopting increasingly ornate body postures, designed to allow my muscle memory to re-engage a long since forgotten skill of serially aliquoting.

There were a few teething problems. For one, I have lost my certainty of action. Never mind the youthful virtue of remembering eight-digit phone numbers. Fading cognitive flexibility has seen me struggle to remember if each and which of each tube had the requisite additions. Also, my fading light sensitivity means I could only pipette small microlitre volumes, with the assistance of the midday sun supplementing the lab’s artificial lighting.

Not to say, like all greats, I did not have one last master play in me. This involved a combination of long distance and short distance vision. In the former, I would initially have my glasses on to read the label on a bottle at a distance and to assist me in being able to remove the screw top lids. This would be followed by a series of jerky neck movements that allowed my facial furniture to slide down my nose, so I could micropipette with the acuity of a short focal plane. It’s pretty effective and despite looking quirky, also looks good. Indeed, if you can perform the O’Toole you are almost guaranteed entry to the Berghain club in Berlin (https://tinyurl.com/ydxy-8t9j).

The conclusion of the pipetting sojourn is that fading motor co-ordination and eyesight indicate my legs are gone. Bench science is for the young.

Forever young

I have found succour in the utterances of a recent noble prize winner, who advised “Passion is a young man’s game, older people gotta be wise”. On reflection, it is such wisdom, displayed by those veteran players from yesteryear that I found so appealing. They were more like philosophers than hard-running athletes. This promotes the idea that my future might depend on developing a quick line in wisdom. I propose going to the lab, resting my chin on my hand and proffering deep thought on existence and pipetting.

The success of this approach is utterly dependent on the passion, energy, skill and commitment of the young colleagues that “can can, doing”. The wisdom is, of course, in first recognising this as a future. I think it can work as long as I am allowed a post-prandial afternoon nap between bouts of being wise. Failing that I will have to find a way to “Stay forever Young”, which despite the beauty of the song may be a forlorn hope (http://www.daily-motion.com/video/xs13ou).

Nero, keep climbing every rung, I guess there is more than one way to keep “yoof” your side and they are doing a fine job.

Bis dann,

FintaNO’Toole
Attending academic conferences is an important and sometimes fun part of a researcher’s life. But it comes at a cost – travel expenses, visa difficulties, time away from work and family. Could online conferences be an alternative?

Academic conferences traditionally involve gatherings of scholars, who share a common interest in a particular scientific discipline. Nowadays, also interdisciplinary conferences are very popular as they bring together people with different research profiles, ranging from basic researchers to clinicians, from physicists to bioinformaticians.

Work dissemination, sharing ideas and both positive and negative experiences are the features that attract most participants. Often, researchers perceive conferences as an integral part of scientific communication, making them one of the most-widely used work dissemination channels, after journals, of course. Conferences are also well-suited as platforms for discovering the latest techniques and spotting new directions in a particular field. Participants are eager to interact with their peers, creating year after year a precious personal network of contacts and acquaintances, which will, at best, be helpful in a grant application or a joint publication, someday.

However, as John Kirwan, emeritus professor of rheumatic diseases at the University of Bristol, UK, recently pointed out in his Nature Careers column: science is all about sorting the wheat from the chaff. Kirwan also paraphrased another respectful scientist, two-time Nobel Prize winner, Linus Pauling, whose dictum was that if you want to have good ideas, you must have lots of ideas and learn to throw away the bad ones.

The same applies to academic conferences: in order to find that fundamentally fruitful collaboration, you usually need to attend a lot of conferences, listen to a whole bunch of ideas and meet dozens of peers. A big time and energy investment, not to mention the money!

Too much noise

Is it really worth it? Donald Nicolson, who has worked in Health Services Research since 2001, and has begun to develop a name in science writing, argues that it is usually not! After attending numerous conferences, he looked at his notes and records and wondered how much they have really impacted his career in the long term. “There are good moments at the conferences but very often unfruitful discussions generate a lot of noise, making it difficult to pick something meaningful for yourself,” explained Donald, who recently published a book entitled Academic Conferences as Neoliberal Commodities, in which he criticizes the current state-of-the-art scientific meetings.

According to Nicolson, what used to be authentic gatherings to sincerely discuss new data and frontiers in the field, have since turned into seen-and-be-seen events, in which ideas, values and reputations are traded like on a marketplace, as one reviewer of the book pointed out. In his book, Nicolson reflects on the usefulness of conferences, particularly bearing in mind the travel costs, the environmental impact, the visa difficulties and the time needed to attend a conference; in addition he also considers further barriers, faced by people with a disability.

Not to forget the inherent inequalities. Senior faculty members, for instance, can often afford to stay in decent hotels, travel with non-low-budget airlines and have dinner with peers in higher-priced restaurants, without too much worrying about the slow reimbursement of the travel expenses from the part of their employer. For junior participants, such as PhDs and post docs, this is unthinkable. They often have to share a room in a local hostel and eat on-budget meals to get the opportunity to pre-
sent their work and start networking with peers. There are many anecdotes that junior researchers, more often than not, invest their personal savings to get to a conference of interest. Plus, being away from one’s family, sometimes for an entire week, and not being able to fulfil one’s responsibilities and duties at home are commonly overlooked, non-material costs of academic trips. Because of all these reasons, particularly the economic ones, academics often are forced to cross off conferences from their yearly schedule. This is even truer for scientists coming from lower-income countries.

What does that mean for the conferences? Certainly, there are less diverse talks and less abstracts submitted, obliging the organising committees to include lower-quality material to attract enough participants and cover all the expenses. In the long run, this practice may lead to a decreasing quality of a given conference, which would make motivated academics rethink their decision about attending it in the future. But organising committees aren’t the only ones suffering intellectual damage in the latter scenario: academics punish themselves when they don’t attend conferences. Being isolated in one’s circle of ideas can leave a researcher’s output rather dry.

**Welcome to e-conferences**

There are voices who argue that in an era of internet omnipresence, there are far better ways to disseminate the academic endeavour to the proper audience. As an alternative to conventional physical research meetings, researchers increasingly meet online, at web or online conferences. Here, attendees show and discuss their work in online presentations, video recordings, documents and chat rooms, without the necessity of being at the venue personally. This approach is much cheaper and takes only a fraction of time. Less travelling also means more time for work or family.

Back in 2005, the CISSE (Computer, Information, System Sciences and Engineering) conference was the first high-calibre research conference in the world to be entirely conducted in real-time via the internet. Ever since then, technology has moved much further and modern communication possibilities support environment-friendly web gatherings that can be followed and participated in, without leaving one’s office chair.

In its main lines, e-conferencing is very similar to a conventional conference. Typically, one registers online by submitting an abstract that will be reviewed by a panel of specialists. Once registered, when the conference starts, you get notified about the opening of a chat room for a real-time discussion, while watching a PowerPoint presentation that is synced with real-time audio. The security of information is guaranteed by limiting the session’s access to registered participants only.

And there are more advantages. Have you, for instance, ever worried that you missed some interesting lecture in a parallel session? There is no such problem in online conferences. Materials are available throughout the entire duration of the conference.
ference (and often even months after) and all registered participants can discuss them in a dedicated chat room, at any time. In some cases, the conference is even archived for future viewing.

**Much cheaper**

Similar to physical conferences, e-conferences issue certificates of attendance and proceedings that are indexed in relevant scholarly databases. This kind of conference post-processing is included in the participant’s fee, which covers all technical expenses (servers, maintaining and development), conference management software and administration. Good to know: the registration fee for an online edition is usually much lower than for a common conference. Fees can be as low as 30 euros for visitors without an abstract, opening more possibility for participation of lower paid research staff and students.

For many of them, this could be a first step toward peer networking outside their institutions. Because of the space and time flexibility, they can get feedback or network with people otherwise unable to attend a distant conference site. It can also reconcile the gap between lack of funding and the obligation for a researcher to include conferences in their curriculum to gain promotion or maintain their position.

Usually in the hands of researchers themselves, it’s possible to task professionals with fully taking care of online conference management. One of these professionals is SCIEMCEE, a web system used to organise and administer science conferences and symposiums held by universities, science and research institutions and corporate entities. It started in 2010 and has hosted more than 50 conferences, so far, ranging from natural sciences, psychology, medicine, industrial engineering to economy, marketing and management.

The average number of attendees per conference is around 100 with the largest one, the Masaryk Conference for PhDs and Young Researchers, gathering 555 participants in one of its annual online editions. “We collect feedback by online forms that are available after every single conference,” said Jiri Kralik, one of the founders of SCIEMCEE and “every feedback is taken into consideration and helps us to improve the system”.

**Only for the young?**

The feedback told them that young investigators are often pleasantly surprised about the ease of the system use, timely presentations, prompt responses to enquiries, proceedings being placed in the Scopus database and high comfort, while attending an e-conference from their workplaces or homes. “A big challenge is to explain to academia that online conferences might help to disseminate their results more effectively. In this respect, the biggest obstacle is elder academics, who are often reserved for novelties in communication,” reflected Kralik, who is otherwise very optimistic about the future of e-conferences. “The number of participants is growing and the proceedings are indexed by several databases. So, the reality already proves that online conferences have their place in the science world and soon will be regular parts of sharing results and knowledge,” he said.

As a further sign that not only scholars are contemplating the online conferencing format for work dissemination is that software developer Adobe put in place a web solution (Adobe Connect) for meetings of up to 100 people. They even offer access from different devices and built-in analytics for any kind of gatherings; academic or corporate. It would be interesting to follow the implementation of this system in industry and also academia, in years to come. For the latter, this solution could be suitable for organising smaller regional conferences.

**Drawbacks of the virtual world**

The cost-effectiveness of online conferences for academics and for the whole scientific community has gained quite some attention in the last couple of years but “as such, online conferences can only tackle some of the issues of the convention-al conferences”, commented Nicolson. He also adds that online gatherings can suffer from much the same intrinsic problems as conventional ones – too much see-and-be-seen dust. Or better: hear-and-be-heard in the www virtual venue.

The lack of face-to-face interaction is a notable drawback with this type of scholarly exchange. “For many people, the main benefit is not to present or listen to talks but to interact with peers on the margins of the conferences. This essential part of the conferences will hardly be recreated in some virtual environment,” commented Nicolson, on the possibility that online chat rooms could soon replace venues and corridors of the conference centres.

Virtual venues are still not perceived as good-enough substitutes for personal engagement. “Unlike at an actual conference, where you are in a physical space and time, an online conference is edited at the click of a mouse. This has benefits but can also rob the person of those serendipitous moments that occur, when he or she endures a person rambling for ten minutes in the conference.
bar before saying something that makes it all worthwhile. There is sometimes gold to be found in noise,” he said. Can we find that gold by attending a conference at the mere click of a mouse?

Maybe there are enough niches for these two conference formats to co-exist or perhaps – to create a symbiosis. A recent experiment with an online supplement to a physical conference looked promising. The Algal Biofuels and Bioproducts conference attracted 384 physical attendees, while the online edition, providing access to the keynote presentations until two weeks after the physical event, attracted a further 354 people, nearly doubling the outreach of the conference.

Parallel events

Another example is also the Beyond Sciences Initiative from the University of Toronto, Canada. This initiative hosts an annual remote conference, covering scientific hot topics with a mission to increase understanding among geographically separate research communities. Therefore, the registration is free and the conference can be attended remotely, by anyone with internet access. The 2nd edition was held physically attended remotely, by anyone with internet access. The 2nd edition was held physically and online, providing access to the keynotes until two weeks after the physical event, attracted a further 354 people, nearly doubling the outreach of the conference.

Good and bad webinars

Popping up like mushrooms are also online seminars or webinars. Some, however, argue that they are not even close to a real-world experience of a lecture and will never be greatly attended. Yet, they persist in the online domain and are becoming increasingly popular. Many biotechs, for instance, use them to advertise their new products and participants, or potential buyers can pose questions and comments in real-time discussions. Tania Sultana, lecturer from the University of Dhaka’s, Bangladesh, Department of Biochemistry and Molecular Biology, attended numerous such webinars and says that she valued no strict schedule, travel, visa or other important expenses while attending webinars. These are the very same conveniences that participants of online conferences cite. Sultana adds that “online courses can be of the same quality as the regular ones but it is not always the case”. The same can be said for online conferences.

At a good conference, the traditional format and the innovation can go hand-in-hand. Looking at the future of scientific gatherings, one can predict a shift towards virtual conferencing but given the value of interpersonal direct contact, there will still be a place for conventional conferences for those scientists, who can afford it. Supplementing physical gatherings with online tools can significantly enhance attendees’ experience and leave a greater impact. For example, some conferences offer mobile apps, which enable the scrolling of the attendees’ roster, biographies and the conference programme by the touch of a finger. Hot discussions don’t have to be terminated because the next talk is about to start. The dialogue can as well be continued through social media, like Twitter, giving a real-time insight and space for reaction – also for those unable to attend.

Corresponding impact

So, as mentioned earlier, if you want to have good ideas, you must have lots of ideas and learn to throw away the bad ones. Experimenting with different virtual possibilities and social media can undoubtedly enrich conventional face-to-face conferences and reach a bigger audience. Over time, accepting useful and rejecting inefficient new practices can hopefully lead us to an enhanced experience of scientific communication, whose real-life impact will correspond with the level of invested time, money and energy to attend them; being held either in conference centres across the globe or running in your preferred web browser.

Ivana Strazic Geljic
A conversation with Corina Logan

“People are Feeling Bullied”

Can we change academic culture through our publication choices? Corina Logan explains the need for researchers to become personally aware of the ethical consequences of how and where they publish their science.

Lab Times: You recently launched the campaign “Bullied into Bad Science”, identifying yourselves as early career researchers, who are concerned about the desperate need for publishing reforms in scientific research. You say younger researchers are often pressured into publishing against their ‘ethics’ and are calling for a shift in academic culture, notably through decisions about publishing choices. In your recent article, “We can shift academic culture through publishing choices” (F1000Research 2017) you describe people in the publishing world as being either ‘exploiters’ or ‘ethical’. Could you elaborate?

Logan: The ‘exploitative’ versus ‘ethical’ publishing distinction is about where the money goes. In exploitative processes, the publishers are usually draining money from publicly-funded research. So, the public funds researchers to do the research. But then, the researchers are giving the research products for free to a publisher – which is most often a publicly traded company or corporation, like Elsevier or Springer – whose profits go to their shareholders. They are making more profits for their shareholders than even Google (SV-Pow! blog, 09/05/2017) It’s insane! All of that money is leaving academia. Moreover, it is usually the case that the public can’t read this research, even though they are the ones who funded it. So it’s a very broken life cycle.

On the other hand, with the ethical publication of a research paper, if there is any money exchanged, it stays inside academia. So, we are not losing the public funds from the research process. Publishers that are non-profit organisations are contributing to academia. There are also some for-profit companies that I would consider to be ethical, for example, PeerJ, because they charge almost nothing to publish articles and they are working to make scientific publishing better for scientists.

When you say they are for-profit, you mean they’re saying we will limit our profit to, say, 1% of our turnover?

Logan: PeerJ are for-profit in that they have venture capitalists, who invest in them. That’s how they got started, so they have to pay back the venture capitalists. But when I talked to the CEO, Jason Hoyt, a couple of years ago, he was saying they are aiming to get publishing costs down to zero for authors because they are thinking that they will do something else to make money, for example, make a software product that they can sell and then use that to make money to subsidise the journal. They are looking at alternative business models to make publishing free. In the meantime, their fees are so low that they are not making a lot of profit. They also reinvest some of their profits to develop ways of streamlining the publishing process.

In your F1000 article, you say that researchers and publishers have a responsibility to the public to provide free access to publicly-funded products, which are a common good. But it’s one thing saying that to researchers, especially if they are publicly-funded; it’s another matter with publishers. There are obviously some publishers, who are only in it to make money out of the whole process – by making access scarcer they can raise the price. You have been giving public talks to increase awareness about scientific publishing?

Logan: In the summer of 2016, I gave a talk about what I had been learning about scientific publishing during the previous few months. This was in the context of a summer postdoc seminar series in Zoology at Cambridge. It was a 20-minute talk followed by a two-hour discussion – it sparked a lot of conversation. There were mostly early career researchers in the audience but also a few senior people. It became apparent that the early career researchers wanted to publish in a particular way – they wanted to publish openly and they didn’t want money leaving academia; being wasted, from our viewpoint. They also felt that they had to publish in particular journals, in order to advance their careers.

However, they also said that if the University of Cambridge was willing to issue a statement saying that it would endorse publishing in particular journals – what I would call ‘ethical journals’ – then that would really help us because, when we are applying for positions and grants, we can say, ‘Look, I published my research in this way because the university encouraged me to do so.’ Rather than coming up against people’s biases about ‘Why didn’t you publish at X or Y journal?’

I’ve presented the talk several times since then and the same issues keep coming up. People feel under pressure to publish in particular journals. Sometimes you can pay for open access at these journals, but not always, and most of these journals do not engage in other open practices that increase research rigour. It’s problematic if we want to conduct rigorous research.

So you wrote your article based on the feedback you received and then started the campaign with researchers in Cambridge?

Logan: There were several of us who were particularly frustrated and wanted to do something about it. At Cambridge, we are doing a lot internally, trying to change how the university is subscribing to journals. And it is not very effective. The changes are not happening. So we thought, ‘Alright, what’s another angle we can use to put pressure on them to change?’ We thought a public campaign would be effective, because it might put pressure on the top from above. And we felt the early career researcher angle was our strongest, because we are a vulnerable group. We are not likely to get jobs in academia because there are so many of us, which means we compete
against each other like crazy. Creating that kind of competition makes it easy to take advantage of us. So, we chose the early career researcher angle. Then we thought we needed a really catchy title, something that the press is going to pick up. So I said what about ‘bullied into bad science’ because, for example, there is a staff survey at Cambridge every few years and what emerged for Zoology (and university-wide) was that people were feeling bullied. I don’t remember the exact percentage but somewhere between 12 and 20% from the Department had either experienced bullying or observed it happening. So what is bullying? Basically, the definition, as far as I understand it, is that you feel pressured into doing something. That word ‘pressure’ I kept hearing from early career researchers – ‘I feel pressured into doing that’. But bullying sounded a little catchier.

You list a lot of anecdotes from early career researchers on your site. Effectively, they say they are being forced to follow certain practices, for example, the logic of the impact factor, where they have to publish in high impact journals if they want to advance their careers. But even then, when they do succeed in publishing in one of these journals, they’re then told that they have to do it again if they really want to succeed. It’s a never-ending pressure to keep doing it over and over again under the menace that you will be ejected. This leads then to the question of what can we do to change the system? You are suggesting eight specific actions. Your first action calls for them to sign the Declaration of Research Assessment (DORA) that came out in 2013 under the initiative of the American Society for Cell Biology. They were making 18 recommendations at that time for changes to publishing practices that were directed to researchers, funding bodies, and finally to the publishers and editors (see LT 5-2013 p.18-23). Were there any specific points you were aiming at?

Logan: We wanted to make our eight actions broader and less specific, so that people could implement them in ways that they felt were more specific to them individually. For me, I think I really like about DORA is that it could mean we are positively selecting for people who are engaging in open practices. DORA presents the idea of judging candidates, based NOT upon publication metrics but rather it encourages people to look at individuals and evaluate them based on their individual qualities. I think this is the key. If we combine valuing a direct assessment of research quality with a positive valuation of open practices, then we can positively select for people that are really engaging in them. This would give a huge incentive to engage in these practices, which would result in a shift in academic culture. That’s what I really see as being the essence of the value of DORA.

I am about to advertise two positions for the first time and I have written two open access points into my job description. I also say that I will not evaluate candidates based on proxies, I will directly assess their research quality – I am going to read their papers, I’m going to read their abstracts, what they write. I am super excited about it and it was so easy to do. It is so easy to implement all of these actions into your regular research programme. The more power I get, now that I am in a position to hire someone, the easier it is. I just can’t believe that all people don’t already do this. It must be that they don’t want to do it or they’re not even aware that they can.

Whenever I give my talk on exploitative versus ethical publishing, even people who are open access advocates, like Peter Lawrence, say that they learn something from my talk, especially about our relationship with publishers and what they are doing with our money. We assume that people are aware of how publishing works but I don’t think most researchers know about all the angles. I know I wasn’t aware of any of this when I started investigating academic publishing a year and a half ago. I had no idea, no clue. But once I began learning, I decided to start to change it.

Did you see the article in the Guardian newspaper about the history of the rise of the modern scientific journal system and the revelation that these practices were developed after the war by Robert Maxwell in the United Kingdom (27/06/17)?

Logan: Yes, it started from one guy. His goal was to be a millionaire and he succeeded by getting us to exploit ourselves. It’s insane how it started. And that we keep it going is even worse!

Do you feel the tide is changing? On the one hand there has been a rise of the open access publishing movement since 2000, notably with the launch of the Public Library of Science. But then you get the impression that the big publishing houses, like Elsevier, have found other ways of tying us down. Do you feel you are part of the New Wave that is now countering that?

Logan: Yes I do. That’s the ethical angle, right? For me, what has been hard to convey to researchers is that on the one hand, there is the open access part, which is about not discriminating against who can read your research. But the ethical angle is about whether we are being exploited by these publishers. It’s the combination of the two that makes the whole ethical life cycle. I think people are becoming more aware now because of articles like the one in the Guardian. Maybe they’ve kind of a bit about it before but they were not willing to do anything about it.

Maybe it’s the circles that I’m in, but researchers are very frustrated with big publishers and some researchers are taking actions to avoid contributing to their oligarchy. I see new journals coming out that are not based at these big publishers but then

"We assume that people are aware of how publishing works but I don’t think most researchers know about all of the angles."

"I kept hearing the word ‘pressure’ from early career researchers.”

Originally from the Seattle area in the US, Corina Logan did her PhD in Experimental Psychology at the University of Cambridge, UK. As a research fellow at the University of California, Santa Barbara, she set up a grackle (an urban bird) field site to investigate their behavioural flexibility. She currently has a Leverhulme Early Career Fellowship (three years) at the Department of Zoology, University of Cambridge. In 2018, she will become a senior researcher at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.
journals get bought out by them and they become dependent. I guess I feel it’s too early, to say whether we are going to be able to get away from these publishers. It really depends on how many researchers decide to make different choices. I hope that we do. I feel lucky that I am able to make different choices. There are several journals where I can publish that I consider ethical.

Companies like Elsevier are now buying up data repositories and research services, like Mendeley; they want to get their hands on every aspect of the research process. They’re trying to own the whole scientific process and then they will sell it back to academia in so many different ways. It’s incredible. That’s what they do. It’s good for business. But it’s not good for us.

Some people would say they are parasitic. But like all parasites, there is a danger they will kill the host.

Logan: That’s a good point. They are definitely parasitic because they get a finished research product for free and then sell it back to us.

Several of the other actions you advocate in Bullied into Bad Science address issues of open practice, not just to publish in open access journals but also to make preprints available in recognised repositories, to openly publish data and datasets, so we can have access to them, to educate researchers about open publishing practices and generally to increase transparency. How open are you?

Logan: In terms of my own research? If I had known then what I know now? When I was doing my PhD, would I have done things differently? During the last couple of years, I have published my code and my data with all my papers. In the last year and a half, I’ve published preprints, so obviously my previous papers didn’t have these open elements. Although thinking about it, I did actually publish my data – even from the beginning. What about negative results? Did I not publish something because there were negative results? I can’t actually think of an example where that happened; and I have published negative results.

Were all of my hypotheses and predictions generated a priori or were they changed after I got my data? From my memory, I think that I did it the right way round but I could be wrong because memory is flawed. If I had pre-registered my experiments, I could have seen what I said at the beginning, before I obtained the data and what was subsequently modified based on the data. I think my research could have been made better by engaging in pre-registration.

You talk about a posteriori hypotheses but we are still allowed to modify our hypotheses in the light of the data, as long as we openly say – look, our original hypothesis was this, then this data was obtained, subsequently we have modified our hypotheses?

Logan: You should say that the post hoc analyses are exploratory. If you want to test them, you would have to do that in a future study.

Many biologists are not well-trained in concepts of statistical power. When designing experiments, they may get confused about whether this is considered to be a good or bad practice.

Logan: That’s true. But that would be taken care of by doing something like pre-registering studies. We should really add pre-registration as action number nine in the Bullied into Bad Science petition.

You have written about the effects of bad practice. You note that in some fields, like medical science and psychology, there are estimates that half of all publications are of no scientific value because these studies have been so badly designed that we can’t really conclude anything from them, and any attempts to try and reproduce them simply reinforce the impression that the underlying research is worthless. This is even more wasteful of resources than having to pay the publishers to publish the papers.

Logan: I agree, and this is where registered reports could save researchers lots of time. I’m learning that there is a difference between pre-registrations and registered reports. Registered reports are where you have a pre-registration that gets peer reviewed. Once it passes peer review, you then collect the data, and then you can write the paper and publish it in the journal the registered report is at. The idea is that the journal has already agreed to accept it because it doesn’t matter what the results are – they have accepted your article on the basis of the proposal that you made prior to doing the experiment. Your hypothesis and methods have been validated as scientifically sound. They have accepted that using these methods, you can test this hypothesis. If more people submitted new studies as registered reports, then unsound research would be rejected before it was conducted.

Pre-registration is where you say these are my hypotheses and predictions and analyses, and then you register them before you have collected any data or provided any post hoc explanation. There’s a record of what you said before you conducted the study and you can cite it in your paper, so others can check it.

Would you like all researchers to pre-register the design and aims of their experiments?

Logan: Absolutely. I’m just in the process of pre-registering my latest experiments. This process helps prevent practices, such as p-hacking and changing the hypotheses to fit the journal after the study was conducted.

Who do you pre-register with?

Logan: The Open Science Framework (https://osf.io). It’s a website that is really nice in other ways, too. You may not only pre-register experiments but you can also use the website to facilitate your projects, either publicly or privately. I have a cou-
ple of private projects, where I coordinate my collaborators on the grackle project. I have the budget there, the project description, how we can order supplies, etc. Everyone can update it and modify the documents as new information comes in, and it is automatically shared with everyone else. It makes much easier to collaborate and coordinate teams. I can also make projects public. I have started putting up my talk slides and conference posters. And grant applications, too. These are public projects that everyone can see.

You’ve put your grant applications online? Are these ones that have been accepted or ones that have been refused?
Logan: These have been accepted.

You are not worried about revealing unpublished information to your competitors?
Logan: Well, one of my projects was the original grackle project but I’ve already published that data. The same goes for my red deer project – that data has also already been published. The pre-registrations can be embargoed for up to four years. But for the one I’m doing right now, which is on social learning, I already did the experiments in New Caledonian crows and now I’m going to do them in grackles, so there is nothing secret. I’m thinking of not embargoing it because no one else works on this species. So I’m safe.

The eighth action on your Bullied into Bad Science site is very interesting because you’re asking for all postdocs and young researchers on short-term research contracts, such as yourself, to be given voting rights in the institutions where they are working. How does this work, for example, in Zoology in Cambridge? Do you feel you have influence over the governing of the department?
Logan: That’s an interesting question. In general, postdocs don’t have much power. In Zoology, postdocs are not allowed onto the Planning and Resources committee, which is the main committee that defines our departmental vision. I have tried to get on it but they say non-permanent staff can’t because we are a temporary group. They want people on the committee, who are going to be here long-term because they will have a long-term investment in the direction of the department. My argument is that the postdocs outnumber the faculty. At Cambridge, in general, we are the largest academic group; therefore, we are doing most of the research in the University. That we get no say in how the university is governed because we are short-term doesn’t really work. There might always be turnover with postdocs but they should be included in university decisions because, overall, you are getting the ongoing average of the group. These average opinions will then be represented on committees. I haven’t had an opportunity to talk to the administrators about this in depth but this seems to be their main concern.

At the university level, apparently all it would take is for the administrator of each department in Cambridge to say, ‘Yes, we’ll let our postdocs become voting members’ and then submit the list of names to the Regent House. If you’re a voting member, you are a member of the Regent House; but if you’re not, you have to get special permission to sit in on the discussions. The president of the postdoc society is not a member of the Regent House and she has to get special permission to sit in on present issues at Discussions. I am a PI, so I am actually a member of the Regent House but my partner is a postdoc and he is not. Some postdocs are members of the Regent House but most are not. We’re saying that we should all be made voting members because we’re a group that needs to be represented.

It’s also about not being ‘token’. For example, on hiring committees in Zoology, there is a graduate representative but there is no postdoc representative. And there is only one graduate representative. From what I’ve heard on other university committees, the token early career researchers cannot get a critical mass and so they are constantly outvoted. Unless you have a critical mass, then just having a token representative won’t change anything either. Which is why I think all postdocs really do need to be voting members. If they are hired and paid through the university and work in the department, why are they not allowed to vote?

This comes back to the DORA issue. If the decisions are always made by the senior scientists, then those who are lower down the system on their short-term contracts have no chance to influence changes in the system. They just have to go on suffering, being pressured, and often lose out on all their years of education and training and research study if they can’t get a job.

Logan: I was just interviewed by a journal for European science students. They sent me the interview questions and one of the questions was about what can students do. Well, undergraduates and graduates are paying tuition fees in the UK – they are customers at the University. This is potentially a powerful position: they could say they do not want their tuition fees to go toward journal subscriptions but to be used for other purposes that they specify.

How do you think the campaign might develop?
Logan: This campaign has been organically unfolding. I’ve never done this before. Every so often, someone will ask for something and we’ll discuss it and decide to act on it. Like the supporters’ letter. After The Times article came out (01/07/17), senior researchers immediately started emailing me, asking how they could support the campaign. It was wonderful and I was so excited. But I needed to find a way for them to do that, so I made the supporters’ letter and asked them to list what actions they are doing right now, to better support us. And some of them are doing amazing things.

What are the next steps? One of the steps is that I am going to write to people, who are influential decision-makers in the UK, because that’s where I’m based, to say here are all these people endorsing these ideas and giving their support. Are you willing to join us? Help us to create change? If so, how can we work together to do that? But really anyone can do this; anyone can take the list of names we have already gathered and the supporters list, and use these materials to show that this is a problem and that we want to do something about it. People can use the campaign materials; however they want, in their own countries and institutions.

Where do we go from here? One student had an amazing idea; she thinks that the University of California should start telling researchers where to publish. Since the University of California has a really strong open access policy, they might also be open to the idea of telling their researchers not to publish at certain publishers. That’s an idea I hadn’t thought of. So, it’s about crowdsourcing. Using human resources to determine what we should do.

Good luck.

Interview: Jeremy Garwood
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cience is not just about improving our future. For some researchers, the fascination lies with discovering more about the history of our planet. From looking at migratory patterns to understanding how some species become extinct, analysis of ancient DNA has become a window into our past.

For Michael Hofreiter, evolutionary biologist based at the University of Potsdam, Germany, there is much to learn from analysing ancient DNA. “We can solve phylogenetic relationships, we can learn about adaptation, about the domestication process, about human evolution and mixture with archaic human populations like Neanderthals, about migrations and population mixtures, about changes in population size over time, and about past ecosystems.” As this list continues to grow, many areas of research can benefit from this work, from anthropology and ecology, to archaeology and palaeontology, to name just a few. „Basically, any field of study that can be supported by the analysis of DNA sequences and works with samples dating to the last 500,000 years,” says Hofreiter.

Perhaps, the most well-known example of what ancient DNA can achieve is the recent discovery of DNA from a hominid knee bone, found in the Denisova Cave in southern Siberia, and presented us with an entirely new Homo species: the now extinct Denisovan Man.

But this is certainly not the only case where ancient DNA is vital. From arctic squirrels and pigs, to Great Auks and fungi, Lab Times investigates a handful of studies where this approach is key to understanding the past and sometimes even re-writing history.

About 30,000 years ago, extensive parts of Europe and America were covered in ice, causing a drop in sea level big enough to expose a stretch of land, connecting northeast Russia and Alaska. This allowed for easy intercontinental travel through what archaeologists now call the Beringia zone. It was the way many animals used to cross between the two continents and it seems the ground arctic squirrel (Urocitellus parryii) was one of them.

30,000-year old squirrels

From that period, there are many fossil records from the American side but evidence is scarce on the Russian side. This explains the excitement when, in 1946, unnamed Gulag prisoners dug up a nest with three 30,000-year old mummified carcasses of arctic ground squirrels in the permafrost sediments of the El’ga river, Yakutia, Russia (pictured). Preservation of the mummified carcasses was so good that even lice were found in their hair. The prisoners handed the squirrels to the Gulag camp’s geologist, Yurii Popov, who in turn gave two to the Zoological Museum, now located in St Petersburg. The last carcass is preserved in alcohol at the Magadan Regional Museum of Local Lore, close to where it was originally found. After a morphological analysis, Russian zoologist Boris Vinogradov classed the squirrels as a new species – Urocitellus glacialis – as they seemed to be very different from modern Siberian squirrels.

After DNA analysis, however, Marina Faerman, based at the Hebrew University of Jerusalem, Israel, and Nikolai Formozov, from the Lomonosov Moscow State University, Russia, proved these animals are very close to arctic squirrels (Urocitellus parryii) and should not be considered a separate species (Sci Rep, 7:42639). This answered one question but created another conundrum as these animals were only supposed to be in the Alaska Peninsula. What were they doing in Russia? Digging a little deeper, the duo established that ground arctic squirrels colonised Eurasia at least twice, in movements connected with glaciation, when cold and hot periods changed where squirrels could live. It’s still possible to see the effects of these migrations in squirrels living in Siberia today, which are descendants of the second group that came from Alaska. The twist to the story involves a small and isolated area on the Kamchatka peninsula, located on Russia’s east coast. The squirrels from this region seem to be descendants from Ice Age squirrels, the last ones to mark the first wave of colonisation in Europe.

For Faerman, this is “a fascinating story of discovery by prisoners of Gulag; the fact that, despite all difficulties in former USSR in the 1940s, these remains have been preserved till modern days. What makes this study special is that it is multidisciplinary and is based on history, palaeontology, modern and ancient DNA of these small mammals. We have been able to suggest an alternative scenario of their distribution in Late Pleistocene”.

Moving to America

Fast forward a few thousand years and humans were also getting more adventurous in their travels, even if that meant walking long distances. For groups living in Russia and Alaska, this included travelling through a ~1,500-km-long corridor, which appeared in the ice, covering most of Canada in North America, allowing a safe journey beyond the Beringia region.

Ancient DNA analysis
A Genetic Time Travel

Join us on a journey into the past, where previously held beliefs will be shattered and records set straight at every turn.
Researchers believe that an ‘ice-free’ corridor opened sometime before 14,000 years ago but when humans actually started using this passageway was hitherto unknown. Mikkel Winther Pedersen from the University of Cambridge, UK, and his team were keen to follow the environment in this corridor by collecting ancient DNA from mud on the bottom of lakes. “We wanted to look at when and which kinds of plants and animals were present in the earliest environment,” says Pedersen. “We know that lakes start accumulating components, such as plant and animal debris, from their surroundings as soon as the land masses become free of ice. And as time goes by, these ‘muddy’ components are stacked in layers on top of each other. By coring down and extracting the stacked mud, we could then obtain a good resolution archive of the environment.”

Results showed that it took about ~1,500 years for the corridor to dry but eventually tundra vegetation and animals, such as bison and mammoth, started appearing. Later animals, such as moose and elk, followed soon after in open for- est, which meant that by 12,600 years ago, the corridor had the resources to support human hunters for the 1,500 km journey (Nature, 537(7618):45-9). These results are of great importance, as they actually go against previously accepted ideas that the earliest groups of humans had managed to cross the ice into America through the ice-free corridor before this date.

Ancient symbiosis

Periods of deglaciation can also be just what dormant fungi, potentially hidden in the soil for thousands of years, need to wake up. This is where the past comes to visit the future, as Brian Pickles, from the University of Reading, UK, believes these ancient mycorrhizal fungi can greatly help modern trees (FEMS Microbiol Ecol, 93(6)).

This is known as the palaeosymbiosis hypothesis and it involves “this idea that modern plants can form associations with propagules of symbiotic fungi that have persisted and remained viable for hundreds or possibly thousands of years”, says Pickles. “We hypothesise that in certain landscapes, such as post-glacial environments or in the rapidly warming Arctic and areas of melting permafrost, access to ancient but viable symbiont inoculum could help dispersing seeds to colonise newly available soils more rapidly,” he further explains. When you consider that seeds of some plants can remain viable for hundreds and thousands of years, it’s not much of a stretch of the imagination to suppose that soil fungi could do the same.

It’s early days but, so far, “analysis of ancient DNA has revealed the composition of historical communities of symbiotic fungi. The next step is to see if any of those fungi remain viable and capable of forming associations when introduced to plant roots”, says Pickles. “Clean extraction and dating of propagules, followed by observing the formation of symbiotic structures from these propagules, would provide solid evidence that it occurs. Then we can begin to examine whether older fungi provide different functions for their hosts than modern ones.”

The idea now is to investigate likely locations, such as buried forests, melted permafrost and glacial forefronts, to collect material for experiments and analysis. “There will be lots of grant writing in the future and we are looking forward to seeing where this research may lead,” Pickles reveals.

Painting bison

By this stage, Palaeolithic Homo sapiens had started producing their first masterpieces in cave art. Animals feature heavily in these paintings and when archaeologists analysed the various bison sketches scattered in caves around Europe, the different styles were often put down to the artist’s interpretation of the animal. After all,
art is quite personal. However, it turns out these men were actually very accurate in their drawings and noticed changes in the bison that we’re only now starting to unveil.

Scientists have many samples of bones, teeth and skulls from aurochs (Bos primigenius), ancestor of modern cattle, and the ‘steppe bison’ (Bison priscus) but the European bison or wisent (Bison bonasus) seems to have appeared out of nowhere about 12,000 years ago. “There are only hypotheses about how they appeared,” explains Julien Soubrier, from the University of Adelaide, Australia. “They could come from the same ancestors as the American bison but at which time and from where is a mystery”.

It turns out that, in this case, it wasn’t a mysterious new incomer from Alaska. Surprisingly, ancient DNA showed the European bison resulted from hybridisation between the steppe bison and the aurochs during Late Pleistocene, resulting in a morphologically distinct form, which has survived until modern times (Nat Commun, 7:13158).

Incredibly, this matches changes in how cave men painted bison, ranging from a form similar to the American bison with heavy forequarters to a slimmer version with curved horns and a smaller hump. “To be able to corroborate our interpretation of genetic data, to be able to match that with cave art that actual cave men painted morphologically forms in the cave in real time, is incredible,” says Soubrier. “It really helped to decipher how things have happened in the past. It’s quite cool to think that cave men identified the hybrid form before we could, because they just observed it in the wild and drew it so well that we can morphologically characterise it.”

To add more detail to the time line and strengthen their hybridisation story, the researcher will continue collaborating with his European colleagues, including a group from Poland, and have recently received funding to analyse a further 100 samples of ancient DNA.

Mixing with the locals

Not long after the cave paintings and the travels to America, Neolithic men finally started getting a grip on domestic animals. Following domestication of sheep or goats in Europe is relatively easy, as there were no wild animals, but the story is slightly more complex in the case of pigs. “This poses the interesting question, in which period and to what extent domestic pigs were introduced from the Near East, and how significant the incorporation of local wild boars into the early farmers’ livestock was,” says Amke Caliebe, based at the University of Kiel, Germany.

Her studies showed that wild boars were not significant at first but at some point between 4,000 and 3,000 BC, farmers started allowing their herds to ‘mix with the locals’ (Sci Rep, 7:44550). “The first domestic animals had a maternal lineage from the Near East. Most likely, they had accompanied the first farmers from the Fertile Crescent to Europe as a kind of ‘starter kit,’” explains Ben Krause-Kyora, also from Kiel. However, “Quite fast after the introduction, the maternal Near Eastern lineage was replaced by a local European. This implies an intentional handling or breeding strategy, as it is more complicated to introduce female pigs into a herd.”

Unfortunately, ancient DNA cannot unveil the reasons behind this change in strategy but it’s interesting to speculate about why females were introduced. “One reason might be that the supply of domesticated Near Eastern pigs was uncertain or that they were very precious and scarce for many farmers. Another possibility is that local wild boars were better adapted to the rougher northern conditions and prevalent diseases than the imported Near Eastern domestic pigs,” says Caliebe.

Reading about animal husbandry

Another team also interested in finding out about animal husbandry comes from the University of York. For a long time, they had been searching for bones with the idea of using ancient DNA to work out medieval farming practices. The problem is that bones get incredibly fragmented and all they had to show after three years was a measly 29 samples. Then, out of desperation, the team had a Eureka moment: “If you really want to look at animal management, the history of western medieval Europe is written on parchment, which is the skin of the animal. You may get thousands of bones fragments but you only get one skin,” explains archaeologist, Matthew Collins. “If you go to a library, a single codex might contain upwards of 30-50 animals and we’re talking about thousands of animals, so we realised that if we’re interested in medieval animal husbandry, parchment was a really good material.”

Understandably, the idea of cutting old historical books did not go down well with librarians and archivists. After some negotiating, however, both sides found a way to work together. Thus, when each page is gently cleaned with an eraser for conservation purposes, the waste products are enough to get DNA samples.

One of the books tested was the York Gospels, a book believed to be brought to York in the year 1020 by Archbishop Wulfstan (bioRxiv 2017; doi: http://dx.doi.org/10.1101/146324). “Documents such as the York Gospels allow for the opportunity to study a collection of possibly contemporaneous animals, which is quite a rare data set in the archaeological/historical record,” says Mathew Teasdale.

Strange practices

Initial DNA analysis revealed five different animals, with four of them being females. What was surprising was the fact the animals were slaughtered at about 6-8 weeks of age. “If you kill females at 6-8 weeks, you don’t have a cow and you don’t have a herd,” says Collins. “More than that, if you wanted to get the mothers milked, in medieval times, the mother would only let her milk down if the calf was present. By killing the calf, you kill the letdown response.” In today’s farming practices, this doesn’t make much sense in terms of animal husbandry and the team is keen to continue with their investigations.

With 120 libraries all over the world wanting to participate in this project, as well as 650 other pieces of parchment collected for analysis, the team is certainly going to be busy in the future. They’re also planning to use this approach to look beyond animal husbandry and also include diseases present, degree of inbreeding,
'Aukward' museum mystery

A more recent, but no less exciting, example of how ancient DNA can help put history straight comes from the Natural History Museum of Denmark. For over 100 years, every visitor, who asked about the two specimens of Great Auks, left without an answer. The mystery around the two birds currently on display started in June 1844, when an expedition commissioned by Carl Siemsen to the Eldey Island, in Iceland, spotted the last two Great Auks (Pinguinus impennis) amongst the smaller birds on the island. Both animals were killed but they never reached Siemsen. Instead, they were sold to Christian Hansen, who eventually passed them on to Möller, an apothecary in Reykjavik. Möller decided to skin the birds and their skins, alongside the preserved body parts, eventually reached the museum in Denmark.

Or did they? The problem is that, at some point, the internal organs and skins got separated, and now, on display at the museum in Denmark, the internal organs are missing their skins. "The unravelling of the mystery surrounding the whereabouts of the skins of the last two Great Auks represents a fascinating element in the story of extinction and human involvement in that process. The mystery has puzzled Great Auk scholars and enthusiasts, and museum curators for hundreds of years," says Jessica Thomas, based at Bangor University, UK. "Many have tried to solve it using the known history of each mount, (such as details of when they were acquired by museums, who the dealers were, the date they were bought, etc.) and suggested possible candidate specimens but no one knew for sure."

These suggested candidate skins have been on display in museums in Bremen, Brussels, Kiel, Los Angeles and Oldenburg for a long time, but it wasn't until now that Thomas and her team was able to analyse their DNA for comparison (Genes, 8(6). pii: E164). "As we were sampling the specimens as part of a larger project that looked at the population genetics of Great Auks from across their range, we were able to kill two birds with one stone – excuse the pun!! – and use the data generated in that to attempt to solve this mystery," says Thomas. Unfortunately, the grand revelation for this mystery is a little bit of an anti-climax. Thomas did match one of the skins, currently at the museum in Brussels but had no luck for the other one. Not to be defeated, Thomas continues the search and already has permission from the Cincinnati Museum of Natural History and Science to sample their specimen, as the history of this bird suggests it to be the most likely candidate.

Raising the dead

Finally, perhaps the most controversial field, where ancient DNA analysis could prove invaluable, involves cloning of extinct species. We already have Hollywood's version of how this would work, with the disastrous attempts to create a theme park of several cloned dinosaurs, who invariably escape to cause devastation and turmoil. Of course, extracting DNA from an insect trapped in fossil amber to create a dinosaur would be impossible but there are more recent extinctions – like the mammoth or the passenger pigeon – which are under debate for cloning.

Even before discussing technical issues, however, the idea of de-extinction opens up a can of worms when it comes to ethical concerns. Questions, such as "What would happen to the animal?" or "Will it be used for reproduction?" need to be answered before any work is done.

For Axel Hochkirch from Trier University, Germany, the main point to discuss is one of classification. This would be relevant in relation to their potential conservation status under national and international law. "From a scientific point of view, it is of course quite exciting. However, the result will not be the same as the extinct species as it will probably not be a perfect copy of the extinct one," says the researcher. "Therefore, we proposed to give de-extinct species a new name or at least a clear label […] to avoid legal uncertainties and help to facilitate decisions as it helps to realise that you are releasing something different than the extinct species."

The debate continues. Time will tell whether this will ever happen. Ancient DNA, on the other hand, will continue to elucidate our past and researchers are even getting more creative about the samples they use for analysis, like Soubrier’s team using dental calculus to understand Neanderthal diet and disease (Nature, 544(7650):357-61); or Hofreiter’s group using human coprolites to time the first migrations to America (Science, 320(5877):786-9).

ALEX REIS
Life’s beginnings are no longer a scientific secret. We know that when an oocyte is inseminated by a sperm cell, it develops into a blastocyst and implants itself into the uterus, where it grows into an embryo. Thousands of scientists have followed this chain of events in mouse embryos or other animal models and many textbook chapters have been written about it – but still some questions remain. How do the cells make decisions and how do they ‘know’ where to go in the distinct layers of the blastocyst – faultlessly, every single time. Or to mention another fascinating phenomenon: If the early blastocyst is cut in two halves, it develops into two perfectly fine embryos – how is that possible and where is the information stored? If only we had a model to test some hypotheses…

This was also the wish of researchers at the StemPhys Center, a collaboration between the Niels Bohr and Panum Institutes at the University of Copenhagen in Denmark. Here, physicists and biologists work closely together to answer some fundamental biological questions with the help of computer modelling approaches. In one of the latest collaborations, the teams developed a model that identifies four simple rules to recapitulate the first 4.5 days in the blastocyst (PLoS Biol, 15(7): e2000737).

Ala Trusina, Associate Professor at the Niels Bohr Institute and the study’s corresponding author, recalls, “The stem cell biologists approached us because they wanted to model apoptosis in the early blastocyst. They had this idea that apoptosis is an important factor that works as error correction, in some way.”

**Overwhelmed by biological data**

Ala Trusina, a physicist by training, came into contact with biology already during her PhD. Now, she combines both disciplines and has gathered a team of like-minded, young scientists around her. With so many interdisciplinary competencies in one place, the group brainstormed how to make a computer model to elucidate the role of apoptosis during blastocyst development. “We were completely overwhelmed by the amount of biological information. For us physicists, it was quite hard to understand all the processes, stages and proteins involved,” she admits. So, they began to translate the basic processes into the physical world.

Their model was supposed to explain how three cell types form and separate into layers. First, there are the cells that will make the embryo in the inner cell mass (the epiblast), then there are the cells of the trophoblast, which give rise to the placenta and last but not least, there’s the primitive endoderm, which develops into the amniotic sac. Starting at the fertilised egg, simple cell divisions result in eight cells after 2.5 days. This was the starting point for Ala and co. They pondered what processes they needed to include in their model to arrive at a blastocyst at 4.5 days – the time point when apoptosis happens.

“We gradually built up the model and found that only four rules are enough to arrive at the blastocyst at day 4.5,” Ala remembers. The first rule is polarity: Some cells become polarised and form a shell of trophectoderm around the inner cell mass on day 3. The second rule is opposition: Some cells in the inner cell mass do the opposite of what the majority of their neighbours does. This is mediated by FGF signalling, which makes cells either express Gata6 (high FGF) or Nanog (low FGF) on day 3.5. Now, we already have a mixed population in the inner cell mass and are ready for the third rule, viz. differential adhesion. This splits the two cell types into two layers (the epiblast and the primitive endoderm on day 4).
Simulating real life

But how can four simple rules be enough to explain the complex regulations that happen during early development? And how to test such a bold hypothesis? The answer is simple – by challenging the system with things that occur in real life. The scientists ran over 200 simulations with known mutations and checked if the blastocyst still developed the correct cell ratios and layers. Silas proudly shares that in the wildtype, they got the right cell ratios in about 96% of cases, while with the mutations, they got the same perturbations as seen experimentally. Ala points out, “Whatever we tested the model against, it matched with what happens in biology!”

With this encouraging validation, the researchers dared to take the next big step: looking into the open question of how the FGF protein works out the right proportion of cells in the inner cell mass. Ala and co. hypothesised that FGF signalling is activated at fertilisation and works as a clock from there on. To confirm their hypothesis, they postponed FGF activation in their model and saw that, concurrently, this also postpones the differential expression of Gata6 and Nanog in the inner cell mass. The model also predicted that this inactivation would result in fewer primitive endoderm cells. In a real mouse experiment, their collaborators were able to confirm these predictions. Ala Trusina stresses, “We found that FGF is part of a clock and hypothesise that the scaling of the blastocyst is regulated by timing from fertilisation. This also explains the phenomenon that when you half the blastocyst at the four-cell stage, you arrive at two completely fine blastocysts with the correct cell ratios.”

Although their model is not the first for blastocyst development, it is perfectly suited to model the scaling of the whole blastocyst. Ala Trusina reminds us that for physicists, each model serves a different purpose. “There is no such thing as a better or worse model. You just want the simplest possible model for your specific question.”

The challenging aspect of this project was also the fusion of biology and computer modelling. Luckily, the team had the right person for this job: Silas Boye Nissen, who has two bachelor degrees, one in biology and one in physics. Still, there were endless discussions with the biologists to understand and implement what they wanted. Ala Trusina shares, “In our experience, it is very hard when you only have two specialists because the language barrier is too high. You always need someone in between to overcome this barrier and to mediate.”

Ala and her team now want to expand their model to capture a few more days of early development. This would allow them to even glimpse into evolution because in the first days of development, the blastocysts of almost all mammals look very much the same. “Later, in humans, the endoderm and epiblast form a disc in the middle of the trophoderm, whereas in mice endoderm and epiblast form a cylinder. Our question is, do you need different mechanisms to get to these two structures or is it only one parameter that changes?”

And Silas mentions another project: “If you just take the first rule, what kind of other biological structures can you make? These could, for example, be sheets or folds as we see them in many organs.” Cultured Purkinje cells, for instance, spontaneously form three-dimensional folds, and a model could help to understand how this is regulated.

Bench and computer work

So, there’s definitely no shortage of ideas for new projects in this small group with two PhD students, a bunch of master students and group leader Ala. Everyone is doing both wet lab and in silico work to find out more about biological processes during development. Ala also works on how cells collectively respond to stress – bacteria under heat shock, for example, which resort to Asymmetric Damage Segregation, a phenomenon also seen in stem cells.

With their great visions to find new ways in understanding fundamental processes, Ala Trusina and her team follow in the footsteps of Niels Bohr, who gave his name to the institute they work in. Bohr used to walk around with Werner Heisenberg, discussing life and science, in the park next to the picturesque old buildings. The very same park is popular with young researchers today, who perhaps also discuss their latest projects and new research ideas with their peers or perhaps just enjoy an ice cream in the later afternoon sun.

Karin Lauschke
Modern tapirs belong to the family Tapiridae and are mostly known for their unusual characteristic of having an odd number of toes: three toes on the hind foot and four toes on the forefoot. “Tapirs represent one of the most peculiar large mammals alive today. They are quite poorly known, mainly because modern species are rare and elusive and, in general, represent only a very small percentage of tropical mammalian faunas,” says Jamie MacLaren, doctoral student in the lab of Sandra Nauwelaerts at the University of Antwerp. “Arguably, one of the most interesting points about these animals is that their limbs are similar to the limbs of the earliest ancestors of other living perissodactyls, such as horses and rhinoceroses – the closest living relatives to tapirs.”

It was exactly this idea – that the tapir’s limbs still resemble its extinct ancestors – that started MacLaren and Nauwelaerts on a quest to find out more. Despite an obvious importance to study evolution within this family – namely, how four toes turned into three toes for rhinos and one single toe in horses – analysis of the tapir skeleton is limited and mostly qualitative.

**Assessing every bone**

To cover this gap, the duo set out to quantitatively assess every bone individually and determine whether it was possible to identify each tapir species from its bones alone. *(J Morphol. 2017 doi: 10.1002/jmor.20728).* After all, four modern species of tapirs – the Malayan tapir (*Tapirus indicus*) and its South/Central American relatives, the mountain tapir (*T. pinchaque*), the Baird’s tapir (*T. bairdii*) and the lowland tapir (*T. terrestris*) – live in quite varied areas, from sea level grassland to high altitude tropical forests.

In their previous study, published in 2016, the team started to analyse the top part of the forelimb, where the main muscles involved with locomotion and support are located (*J Morphol*, 277: 1469-85). This generated so many interesting results that the duo just had to continue the analysis further down the leg. “As we found some locomotor differences in the upper limb, we wanted to ascertain whether this was mirrored in the lower limb, which is more involved in the actual interaction with the substrate that the animal is moving on,” says MacLaren.

The bones for analysis came from museum collections across Europe and North America to be analysed at the Functional Morphology Lab at the University of Antwerp, where the team laser-scanned each bone to create a 3D model. For the researchers, this approach was ideal as scans were done without causing any damage to the bone (sometimes the only one of its kind). In addition, since the scan is complete, the sky is the limit for what can be done with the ‘virtual bone’: share with other researchers, manipulate in every imaginable form or use in computer models of locomotion. As a bonus, jokes MacLaren, “This way we didn’t constantly annoy collection managers for loan extensions!”

“From a broader perspective,” adds the researcher, “we offer museums unlimited access to the digital bone for future study, which, in this modern age, may include 3D-printing for educational outreach programmes, so they don’t have to necessarily send rare or unique specimens halfway across the world and endanger their collections.”

**Small but important differences**

Superficially, results show that tapir morphology is quite similar for all species. This is not at all surprising for four medium-sized quadrupeds, which are all from the same family. Looking a little deeper, however, small but important differences come to light; not only in the top forelimb (humerus, radius and ulna, as discovered in the 2016 paper) but also on the hand and wrist (carpals and metacarpals).

The most obvious difference observed the Malayan tapir (*T. indicus*), the ‘chubbiest’ of modern tapirs. So far, it’s been accepted that, despite having four toes in the forelimb, tapirs mostly rely on only three when walking. However, rather unexpectedly, MacLaren found evidence this animal is able to support its own weight on all four functional toes. After all, when living around muddy riverbanks, using all toes is a good way to avoid sinking into cold and wet mud. “Interestingly, the fourth toe of *T. indicus* is much more robust and capable of weight-bearing than the same digit in the other species, and we hypothesise, therefore, that this species unequivocally uses its fourth toe when it is moving through its habitat,” says MacLaren.

On the other end of the spectrum, the slimmer and smaller mountain tapir (*T. pinchaque*) prefers steep forested slopes. In this case, MacLaren found a thin forelimb with muscles attached closer to the joint. These are ideal for rapid movement, if you’re a small tapir trying to escape cougars and jaguars.
uars in a dense forest. There were also adaptations to a life spent running on uneven and difficult terrain, like a braced neutral position, where shoulder muscles work as shock absorbers and joints are adapted to work under the pressure of climbing up and down. “These three adaptations alone may not initially be of interest but together they suggest to us that the mountain tapir has modified its limb to perform better in the species’ natural habitat (high altitude cloud forest with unstable substrate and inclined slopes) in subtle but significant ways,” says MacLaren.

Then there was the Central American or Baird’s tapir (T. bairdii). In contrast to the Malayan tapir, MacLaren found a small fourth toe with limited use during locomotion. “This suggests that Baird’s tapir, as well as having a bizarre skull, seems to be favouring locomotion with only the three central toes of the forelimb and the fourth toe seems to be of less importance for locomotion in this species than others. It seems to be doing things with its skeleton in a slightly different way to the other tapir species,” says MacLaren. “Obviously, this will need to be tested empirically with live animals to confirm the morphology is providing a true signal but we are confident, based on the results of this analysis, that the

Baird’s tapir will demonstrate differences to the other modern species in this regard.”

A family picture

The fourth and last tapir under scrutiny was the lowland tapir (T. terrestris). These animals don’t seem to have any particularly distinctive features on the forelimb but a look at this tapir’s family tree throws up some interesting observations. Current consensus accepts that tapirs originated in Asia and the ancestors of the Malayan tapir separated from its New World ancestors, sometime between 20 and 30 million years ago. It should not come as a surprise then to have such a strong division between the Asian and New World species (T. terrestris, T. pinchaque, T. bairdii).

When you start looking just at the American species, however, their relationship becomes a little fuzzy and the debate continues as to which species migrated to what part of America, and when. What researchers know for sure is that the mountain tapir (T. pinchaque) is very closely related to the lowland tapir (T. terrestris) as they only split between one and four million years ago. Yet, their bones are very different. For MacLaren, this is most likely a consequence of their different choices of habitat: forest with some open grassland for the lowland tapir vs. high altitude boggy forests for the mountain tapir. In contrast, bones belonging to distant cousins, lowland tapir and the Baird tapir, were sometimes so similar that it was virtually impossible to separate the two species. Despite the longer separation (about ten million years), these animals remained in similar habitats and about the same size, which may explain the similarities.

“Unfortunately, the divergences between the four tapir taxa alive today are so deep in time that any explanations on the evolution of tapir locomotion would be dubious at best,” says MacLaren. “Fortunately, some of my recent work in the USA, looking at extinct tapir species, is beginning to fill in some of the gaps and will, hopefully, provide a broader outlook on the variation of locomotion in these enigmatic animals.”

Keep the ball rolling

When asked about future plans, MacLaren is keen to continue studying tapirs. “I feel like I have started the ball rolling, and I would be very interested to further investigate the comparative morphology of tapirs and the earliest ancestors of horses.” The idea is to use tapirs as a morphological and mechanical analogue for ancestors of larger members of the perissodactyl family, such as rhinoceroses and titanothere. In the long term, “Incorporating morphology, biomechanics and 3D modelling to answer questions in evolutionary biology and palaeontology is what I would like to do,” concludes the researcher.

Alex Reis
Every winter, northern elephant seals make their way to the beaches along the west coast of North America after spending most of the year in the Pacific Ocean: it’s breeding season. Males arrive first, in early December. Those days alone, without the females, shape the social hierarchy, defining the mating success of each one of them later in the season. Females come ashore around mid-December and, those who are pregnant, give birth soon after their arrival. They nurse their single pup for about forty days and will accept copulation only at the end of the lactation period. Therefore, it’s from mid-February to early March when the mating finally takes place and the dominant males can enjoy the status for which they have fought.

This individual social status is partly established, based on the outcome of physical confrontations between them. But these heavy creatures cannot afford to be constantly fighting. It is costly and bloody; tougher, given the long period of fasting imposed on them during the whole breeding season, as they do not leave the land to forage at sea. Thus, during these early physical encounters, they also interact using other cues. Being able, later, to use these signals to identify the social rank of the rival, without engaging in a fight, might be handy.

**Seals and their noisy recognition system**

One of the signals used by these males is vocalisation: a series of loud claps that are part of the encounter ritual between them. Isabelle Charrier, an associate researcher at the Paris-Saclay Institute of Neuroscience in Orsay, France, together with colleagues from the Bioacoustics team in France (a group of researchers based in Orsay and Lyon, working in different areas of vocal communication) and scientists from the University of California, Santa Cruz in the USA, want to understand how these acoustic cues allow recognition among members of these colonies. Charrier herself has been interested in this type of communication for almost two decades. After a PhD, focussed on studying mother-pup vocal recognition in fur seals, she has devoted her research to understanding vocal communication in pinnipeds, the clade to which seals belong.

Pinnipeds look like a good model for studying vocal communication: they appear to be quite noisy! But Charrier’s interest in these animals is also due to another aspect. “They are very good mammalian models because different species show different social structures. You can find pinniped species that are almost solitary, while others are highly colonial: there is a huge scale in the social structure,” she explains. It’s the same with their breeding system: you’ll find monogamous species, like the spotted seal, and highly polygynous ones, such as the northern fur seal. Charrier is, hence, interested in studying how social structure in pinnipeds shapes their recognition system. She has been involved in projects researching olfactory and visual recognition but focusses mainly on vocal communication as she believes acoustics is probably “the most efficient sensorial modality” in this context.

**All guys are not the same**

The northern elephant seals (*Mirounga angustirostris*) belong to the social and polygynous type. While on land, males...
establish the social hierarchy that determines the role of each of them within the female harems. For each harem or group of females, there is one alpha male – the highest rank, the lucky one with the best access to females – and a group of beta mid-ranking males that try to steal the position from the alpha males. These beta males are usually found in flanking positions relative to the female congregations. A third group are the younger sub-adult males, also known as peripheral as they stay outside the harem.

“They are watching and learning about the male strategy but always avoiding the big males. Sometimes they sneak into the harem and try to mate with the females but they are not really successful,” Charrier explains.

The competition for the females, thus, takes place mainly among the big guys. The fights are more common at the beginning of the season, when they establish their social status, and also at the very end, “It’s their last chance to mate,” affirms Charrier. But if the exchange of vocalisation and visual cues is sufficient, they’ll stick to that while still being very close. So, one of the questions that Charrier and her colleagues had a few years ago was precisely how these males assess each other. Based on the acoustic displays, do they associate traits in their rivals’ voices with size or dominance status or do they recognise each particular individual?

Who is who on the beach

In the animal world, physical features of an individual sometimes encode information about other attributes. In terms of acoustic displays, for example, the frequency of calls in frogs and toads is an indicator of body size, and male baboons give a two-syllable call (the memorable wahoo) that is correlated with age and social rank.

Given the importance of vocalisation in elephant seal males, the research team wondered whether qualities of the voice could be associated with physical details or social status. They recorded the vocalisation of different males, calculated size and age using photos with a calibrated scale and measured the social rank by observing different social interactions. “We basically scored the loser and the winner of each vocal interaction and, based on this, identified a particular individual as a high-ranking or as a subordinate male,” explains Charrier.

They found a correlation between certain vocal features and body size (e.g. larger males emit lower frequency calls) but no acoustic parameters linked with dominance or indication that body size correlates with social rank. Nevertheless, when the scientists performed playback experiments – previously recorded calls now played through speakers close to the males tested – they found that vocal features were not really relevant for them to make a decision on fighting or retreating. While beta males go away when they hear a familiar dominant male and attack if a call from a subordinate male is broadcasted, they don’t show this pronounced response when they are exposed to calls from unfamiliar males (e.g. recorded from a distant colony) (R Soc Open Sci, 2(8):150228). Previous social knowledge seems to be essential, “They need to really know each other individually. We showed that these guys know who is who on the beach,” confirms Charrier.

Leaving or fighting: rhythm and timbre matter

These results led to the question of how they recognise each other. Acoustic analyses on the calls showed that each individual has its own consistent vocal signature: a particular rhythm, the pulse rate of the call, and timbre, the feature that differentiates a high-pitched from a low-pitched voice. So, what happens if one modifies these properties?

Charrier and her team altered calls from dominant rivals and tested them on the beta males familiar with them, expecting to observe the retreat behaviour, if the call was still recognised as coming from a threatening neighbour. Using specialised software, they modified first the rhythm, by changing the number of ‘claps’ per second, and then independently the timbre, by re-scaling the spectral parameters. The researchers broadcasted both types of modified calls and evaluated the behavioural response of the tested males: would they respond to their dominant rivals’ natural calls when they are slightly modified?

No. They barely reacted to them and in some cases even ignored them: the subordinate males showed to be sensitive to these changes. The alteration of rhythm and timbre also modified the response, suggesting that these two characteristics are required for individual vocal recognition (Curr Biol, 27(15): 2352-6).

Only wild mammal known “to feel the beat”

This ability to recognise and memorise rhythm has rarely been observed in other non-human mammals. The only other mammalian species that has shown the ability to recognise tempo without training is the bonobo: an individual studied in a zoo could spontaneously match and synchronise up their drum strikes, to a certain degree, with a human drummer. But the work of Charrier and her colleagues is the first to show the relevance of tempo in a wild mammalian species for a specific biological purpose. “Elephant seals are very sensitive to this pulse rate and that’s new for mammals, given what we know so far,” she says.

The team is also currently doing some work on elephant seal sub-adult males (the young peripheral ones) to better understand their behaviour during the breeding season and investigate how they assess the other males. They have already performed some playback experiments that are currently under analysis. “We would like to know if they show the same strategy and see whether, for example, they can estimate each other’s age from the vocalisation.”

This year, the team will also start a project on mother-pup recognition in this same species. We will stay tuned, to learn whether the fascinating sense of rhythm in the northern elephant seals is also present outside of the fierce mating competition.

ALEJANDRA MANJARREZ

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Especially Northern Europe, with several specialised research centres, is strong in pain research. Neuropathic pain and migraines are the discipline’s hottest topics.

It’s not an exaggeration to claim that almost everyone has made their own experience with pain – the occasional headache or migraine, stomach ache or the stabbing pain after accidentally stepping onto tiny toys, scattered in a child’s room. Unless you are one of the very few people (there are about 20 cases in the literature), who suffer from congenital analgesia. These people are not able to perceive any form of physical pain.

At first thought, this insensitivity to pain may sound like something good but one should not forget that pain has an important function in our body: it tells us to stop doing the things that could potentially harm us. “Internal injuries are the ones I fear the most. Appendicitis is what really scares me. Usually, whenever I have any type of stomach issues or a fever, I go to the hospital just to get it checked out,” a congenital analgesia sufferer told the BBC in 2012.

Scientists studying the condition showed that a mutated SCN9A gene is responsible. This gene normally codes for the NaV1.7 sodium channel, expressed in nociceptive neurons at the dorsal root ganglion in the spine. The mutated gene, however, generates only non-functional alpha subunits, preventing the ion channel from forming properly. “The thing is, with our condition, a lot of people see us and they might assume that we’re healthy. But they have no idea that my body could give out at any time that I ache all over.”

For the majority of humankind, however, pain – in its different forms – is a more or less constant companion and thus, it’s no surprise that many scientists are devoted to this area of research. Before we reveal, who are the most-cited pain researchers in Europe, we first have a look at the nations’ performance. For this part of the analysis, we solely relied on ‘specialist’ journals as selected by the Web of Science database. The reason being that the database cannot reliably fish out pain-related research papers from multi-disciplinary journals, such as Nature or Science. This restriction to specialist journals did, however, not apply to the most-cited authors list.

As usual, the top spots of the nations’ performance ranking go to Germany and England. The two nations are very close, with regard to total number of citations – Germany has just 1,000-odd citations more than England. But there is a huge difference between the two nations, when focussing on the citation-per-article ratio (11.2 vs 19.3). England, thus, should be named the true top performer in pain research – also, because only Scotland (21.0) managed to obtain more citations per article on average. The top 5 is completed by Italy, The Netherlands and France. Portugal in 19th spot deserves a special mention. Six years ago, when we did the last ranking round in pain research (LT 4-2011), the South European country had only 45 papers and 222 citations to its name. Now, they have multiplied their total citation result tenfold.

Globally, it’s the same picture again and again. European researchers write more papers and gather more citations but, on average, publications by their US peers are cited more often.

Neuropathic pain in the research spotlight

This brings us straight to the discipline’s most-cited papers. This time, the hottest topic is pretty clear. Four of the five top papers are about neuropathic pain – pain caused by injured nerves. Interestingly, not just one but many conditions can lead to neuronal damage, such as diabetes, lupus, rheumatoid arthritis or alcoholism. The two papers in spots 1 and 2 explore pharmacological options for the treatment of neuropathic pain, in general. And the other two papers are about diagnosis, assessment and/or pathophysiological mechanisms. Only the fourth-most-cited paper does not revolve around neuropathic pain, in particular.

Who are these authors, writing highly-cited papers in pain research? Our top 30 most-cited pain researchers in Europe might give us a hint. In contrast to many other publication analyses, identifying pain researchers was not so hard. Wherever we read “pain”, “headache” or “migraine” in the title or abstract of an article, we considered the associated authors to be suitable for our ranking.

Our top 30 showed that one can approach pain from many different scientific angles: psychologically, physiologically, neurologically or pharmacologically. And also from many different geographical locations – although Northern Europe turned out to be a top destination for pain researchers. Three of our most-cited scientists have their home institution in Norway, six in Denmark and one in Finland. When it comes to female top researchers, we
again have good news. Among our top 30 are not less than six women – a comparatively good quota.

The top two places are firmly in the hands of Norwegian pain researchers, Lars Stovner (1st) and Timothy Steiner (2nd), both from the Norwegian University of Science and Technology, NTNU, in Trondheim. The duo gathered many of their citations with large, population-based studies, such as the Global Burden of Disease studies, which found, amongst other things, that “migraine is the third cause of disability in under 50s.” Stovner has also established the Norwegian Advisory Unit on headaches in Trondheim, while Steiner is the founder and director of the Global Campaign Against Headache.

Stovner and Steiner are not the only scientists fighting headaches and migraines. Among our top 30 are quite a few more. For instance, Jes Olesen (4th) from the University of Copenhagen and the Danish Headache Center. In a 2010 article in The Lancet, Olesen complains about the undervaluing of migraine research. “There is a tendency to disregard it because people think, well my wife has migraines, too, but she takes care of everything and she does her job, so it’s not a bad disease. They don’t grasp that it’s an extremely common disorder and you have it in all kinds of severities. (…) We still haven’t got through to the general decision-makers that they could actually get a lot out of their money, if they invested in headache research.” Little funding didn’t deter Peter Goadsby (7th), Tobias Kurth (8th), Michel Ferrari (18th), Arn van den Maagdenberg (20th) and Arne May (27th) from pursuing research on migraine and headache, either.

Other pain researchers are dedicated to finding relief for sufferers of neuropathic pain. Ralf Baron (3rd) and Claudia Sommer (9th) are two of them. Troels Jensen (13th), who’s interested in the pathophysiology of diabetic neuropathy, founded the Danish Pain Research Center, located in the “beautiful surroundings at Aarhus University Hospital”, in 1994. Also interested in neuropathic pain are Rolf-Detlef Treede (14th), Maija Haanpää (26th), Andrew Rice (28th) and last but not least, Nanna Finnerup (30th), who’s also associated with the Danish Pain Research Center.

Cancer pain, back pain, gastrointestinal pain

There are also many other types of pain: surgery-associated pain, for instance. Henrik Kehlet (5th) is “the most well-known surgeon among anaesthesiologists”. Stein Kaasa (11th) studies cancer pain, while Asbjørn Drewes (23rd) focusses on gastrointestinal pain. A rather common type of pain, back pain, is addressed by Bart Koes (10th) and Maurits van Tulder (15th). In a Cochrane Review, van Tulder scanned published research for herbal remedies against low back pain. *Harpagophytum procumbens* (devil’s claw), *Salix alba* (white willow) and *Capsicum frutescens* (e.g. piri piri) seemed to have some effect but as van Tulder must attest, “the quality of reporting in these trials was generally poor”.

A fourth group of highly-cited pain researchers studies pain from a more pharmacological or neurological perspective. Pain medication is the topic of interest for Andrew Moore (12th), Gerd Geisslinger (21st) and Sheena Derry (24th). Pain perception, analysed by neuroimaging, is Herta Flor’s (17th) and Irene Tracey’s (19th) area of expertise.

Whether the decision makers will respond to the calls for a higher appreciation of pain research or not, one can be sure that our top 30 scientists and all the others, who didn’t make our ranking this time, will spare no pains to take ours away.

Kathleen Gransalke

### Europe...

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Articles appearing between 2009 and 2015 in ‘Pain Research’ journals as listed by *Scimago* and Clarivate Analytics’ *Web of Science*. The citation numbers are accurate as of August 2017. A country’s figures are derived from articles, where at least one author working in the respective European nation is included in the authors’ list. Israel is included because it is a member of many European research organisations and programmes (EMBO, FP7 of the EU...)

### ... and the World

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### ...and Papers

1. **Attal, N; Cruccu, G; Baron, R; Haanpaa, M; Hansson, P; Jensen, TS; Nurminko, T**
   - EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision.
   - *European Journal of Neurology* 17(9):1113-1118 SEP 2010
   - Citations: 578

2. **Finnerup, NB; Sindrup, SH; Jensen, TS**
   - The evidence for pharmacological treatment of neuropathic pain.
   - *Pain* 150(3):573-581 SEP 2010
   - Citations: 464

3. **Baron, R; Binder, A; Wasner, G**
   - Citations: 462

4. **Hjermstad, MJ; Fayers, PM; Haugen, DF; [...] Fainsinger, R; Aass, N; Kaasa, S**
   - Citations: 385

5. **Haanpaa, M; Attal, N; Backonja, M [...] Sommer C; Smith BH; Treede RD**
   - NeuPSIG guidelines on neuropathic pain assessment.
   - Citations: 382

Citations of articles published between 2009 and 2015 were recorded up until August 2017 using Clarivate Analytics’ Web of Science database. The “most-cited papers” had correspondence addresses in Europe or Israel.
Europe’s research institutes

The Champalimaud Centre for the Unknown

Sitting proudly, where once Portuguese explorers set out to discover the world, the Centre puts Portugal once again in the limelight for new discoveries, this time of a scientific persuasion.

The Champalimaud Centre for the Unknown is part of the Champalimaud Foundation, the brainchild of millionaire entrepreneur António de Sommer Champalimaud. Initially hosted at Oeiras’ Instituto Gulbenkian de Ciência since 2007, this research institute finally gained its permanent residence, in Lisbon in 2010, with a brand new building covering an area of 60,000 m² facing the River Tagus. The building includes not only the research laboratories situated in the upper floors but also a clinical centre as well as an indoor tropical garden at the heart of this structure. For architect Charles Correa, the building is more than just its four walls, it pays tribute to the Portuguese history, to journeys into the unknown.

Fifteen century sailors and explorers now give way to teams of researchers, coming from around the world to access some of the most advanced equipment in large, open plan labs, in a building especially designed for research into cancer and neuroscience. Having joined the neuroscience programme about eight years ago, neuroscientist Carlos Ribeiro became leader of one of these teams. His group studies how the brain ‘reads’ the body’s nutritional needs, which influence how animals decide what to eat. Recently, they unveiled two different bacteria present in the gut of the fly, which can dramatically alter what they pick for lunch (PLoS Biol, 15:e2000862).

A collegial and friendly place

“I came here”, says Ribeiro, not only because he can “work with amazing colleagues in a very collegial and friendly environment” but also because “we have the support of a generous and visionary institution – the Champalimaud Foundation – giving young people the opportunity to do cutting edge research in a very free environment by supporting them financially”.

With views of the gardens, these patients are treated in a welcoming and relaxing place that looks more like a luxury hotel rather than a hospital.

Another interesting characteristic of the Centre is their focus on outreach activities, which are mostly run by students. They organise events with several speakers, as well as something extra to offer science in a slightly different manner. “For example,” says Ribeiro, “I did one on food, where I was one of the speakers and then a very famous sushi chef came here to speak.” Students also organise events with interactive games, which usually sell out in a question of minutes. “Although the faculty actively participates in these events, the innovation and the motivation comes from the students,” adds the researcher. “We do a lot of that and it’s a lot of fun to interact with the public.”

Part of public life

Continuing their outreach approach, there are several public areas scattered around the centre, from Darwin’s Café to the interior tropical garden, allowing the public access to what’s happening at the Centre. “I wouldn’t say that we bump into people all the time but we’re part of public life”, says Ribeiro, “and that is very important, especially in a place, which doesn’t really have a long standing tradition in doing science, like Portugal. I think it’s important to have a place where people see that we are able to attract some people internationally to come here and do good science.”

With two new research programmes in behaviour and cancer recently started, the future seems bright for the Centre of the Unknown. For Ribeiro, who intends to stick around for the foreseeable future, the credit must go to the Foundation’s courageous and bold decision to get young people and give them the opportunity to create something new. Competitively select and then empower new people to come in with new ideas and they will stay here for the long term. “I think the Foundation has the right vision, to support discovery science, which not only in the short term but also in the long term, will end up being really important. The idea is to change the life of people, not only tomorrow but maybe in ten years. As long as the Foundation has this vision and is able to translate that to recruit the best people and support them, this place has a very bright future. We’re very lucky to be able to work here and Lisbon is an amazing place to live.”

Alex Reis
Is the biotech sector overrated?

2017’s Deal Dullness

Financial figures published by Bloomberg a few weeks ago are worrying the biotech industry. According to the US business news provider, global biotechnology mergers and acquisitions (M&A) activity has slowed down drastically in the last nine months. Whilst in 2016 all takeovers in summary (termed by Bloomberg “deal volume”) still reached an equivalent of €29 billion, this year’s deal volume of just €10 billion worldwide has been two-thirds lower, so far.

Bloomberg stated that “global biotechnology mergers and acquisitions are headed for the lowest annual level in four years”, adding that one possible reason for this could be that, “potential buyers, such as pharmaceutical giant Pfizer, await clarity surrounding US President Donald Trump’s promised tax reform”. And that’s why the pharmaceutical industry in the USA and elsewhere is becoming more and more reluctant to take big acquisition risks.

Other experts support this view. Jérôme Contamine, French Sanofi’s CFO since 2009, stated a few weeks ago that, “biopharma asset prices are pretty high”. And Bloomberg columnist, Max Nisen, told us in July that he is afraid that, “2017 could be the worst for M&A in the sector since 2013”. Huge mergers, such as the 2016 takeover of San Francisco-based Medivation by Pfizer for €12 billion, or Abbvie’s €8.5 billion purchase of the formerly unknown cancer research startup Stemcentrx (also based in San Francisco), are not in sight and rather unlikely to happen still this year.

Is Europe’s biotech industry disenchant- ed as well? Yes and no. In July 2017, for example, an attempted €171 million takeover of Berlin-based diagnostics provider Epigenomics by Chinese Cathay Fortune failed. On the other hand, Johnson & Johnson bought Switzerland’s blood pressure specialist, Actelion, for a whopping €25 billion in January this year, to feed the US pharmaceutical’s pipeline with Swiss orphan disease drugs. Given the fact that the Actelion deal is the largest European pharma merger since 2004, the biotech future isn’t looking as dark as Bloomberg would have us believe. Although Jérôme Contamine and many of his Big Pharma colleagues may be right with their impression that a number of biotech companies are quite overvalued.

W. Koeppelle

Merck/MSD assimilates German start-up Rigontec

It’s not the biggest deal for US giant Merck/MSD, but a decent appreciation for the ambitious German biotech industry: For €115 million up front cash and an additional €349 million in possible future payments, the Munich-based, early-stage cancer therapy startup, Rigontec, becomes part of the American pharmaceutical group.

Rigontec, once founded at the university of Germany’s former capital, Bonn, focusses on immuno-oncology therapies. The small company is just three years old but had raised nearly €30 million by 2016 from illustrious VC investors, such as Boehringer’s Venture Fund and Wellington Partners Life Sciences.

Christine Schuberth-Wagner (see photo), who serves as Rigontec’s Scientific Head, formed the academic spin-off in January 2014, together with her colleagues at that time, clinical pharmacologist Gunther Hartmann and immunobiochemist Veit Hornung.

Their vision was to develop novel RNA-based immuno-oncologics by using the RIG-I pathway, named after the intracellular receptor RIG-I that recognises short RNA strands and is involved in RNA-virus detection as well as in the regulation of the human immune response. Rigontec’s approach in cancer immunotherapy is, “to induce both immediate and long-term antitumour immunity”, according to a recent press release. Their lead drug candidate, RGT100, is a bifunctional RNA molecule, being tested at the moment in a first-in-human study in 54 patients with solid tumours and lymphoma. The first test results are not expected before December 2019.

To date, however, the German’s concept of inducing anti-tumour immunity, followed by significant tumour regression, has been proven only in animal models. And whether their second mainstay, RNA therapies for the treatment of infectious and inflammatory diseases, will also work, has yet to be shown.

W. Koeppelle
Sanofii and Regeneron disentangle

Separation in Part

Surprisingly, French drugmaker Sanofi has allowed a fruitful and longstanding contract with Regeneron to expire. Is this a planned exit, or was it prompted by unknown deeper problems? For the time being, there’s a second contract.

It was in 1988 that Leonard Schleifer met with Merrill Lynch venture capitalist George Sing in a Chinese restaurant in Manhattan. On a napkin, they entered into a contract to start a biotech business with $1 million seed funding. And in doing so, twelve years after the legendary incorporation of biotech pioneer Genentech, another brilliant startup project took its first crucial step. Schleifer had laid the foundations of Regeneron Pharmaceuticals, now one of the “most innovative” US companies according to Forbes, that would one day make him a billionaire.

Do it like Genentech!

Schleifer, born in 1953, was then a young assistant professor in neurology. He had observed Genentech’s pioneering results in recombinant DNA technology since 1977, when the South San Francisco-based company expressed a human gene in bacteria for the first time, with the aim of producing the hormone somatostatin (soon also human insulin and human growth hormone) genetically. However, Genentech’s leadership didn’t take charge of diseases of the nervous system, and so neurologist Schleifer decided to step into the breach. Under the scientific leadership of his companion, six-years-younger George Yancopoulos, an exceptionally gifted scientist of Greek descent, Regeneron started to work on growth-factor proteins to treat Lou Gehrig’s disease (Amyotrophic lateral sclerosis, ALS).

However, the relevant clinical trials failed. Disenchanting years followed, and it took until 2008 for Regeneron’s first therapy, Arcalyst (to treat a rare autoimmune disease) to finally work and receive approval from the FDA. After twenty years of disappointed hopes and running out of money, Schleifer and, “the superstar of his generation” (Forbes), Yancopoulos, reached their first milestone.

The 2007 Sanofi deal

But Schleifer wouldn’t be called, “one of bio-tech’s shrewdest dealmakers”, if he hadn’t sought further options. As early as 2007, his company inked a long-term research partnership with drugmaker Sanofi. Thanks to this pact, Sanofi paid out $100 million a year up to 2010, and then around $160 million a year until 2017. The French pharma group obviously saw enormous potential in the Americans’ technology. Their hunch was correct and five experimental drugs entered clinical tests in the first two years of the contract alone. Since then, the collaboration has created major successes, including Praluent (to lower LDL cholesterol, approved in 2015) and potential blockbuster drug Dupixent (recently approved). Sanofi also took a proper stake in Regeneron, and raised it in 2014 to 22.5 percent, thus becoming its main shareholder.

But then, Regeneron surprised the pharmaceutical world with their laconic announcement in September that, “the company’s antibody discovery agreement with Sanofi will end on December 31, 2017 without any extension”. Wow. A huge deal, worth more than a billion dollars so far and with several successful outcomes, won’t be extended. Why? Speculation is rife (and neither Regeneron nor Sanofi’s new CEO, Olivier Brandicourt, will tell us), but this move is definitely not a pleasant one for Regeneron.

But at least it won’t be a death blow. Two years ago, in July 2015, both companies committed to another collaboration, “to discover, develop, and commercialise new immuno-oncology drugs”. This deal has the potential to generate even more than $2 billion for Regeneron.

Winfried Koepelle
**BGI goes public, and everybody asks, why?**

**Has Beijing found the Biotech Accelerator?**

More and more Chinese biotech companies are on their way to the global market. European and US competitors are watching the new kids on the block with suspicion, regarding their opulent financial situation.

This story is a good example of their aim.

In 1999, the Beijing Genomics Institute research centre was founded, to produce 1% of the human DNA sequence as China’s contribution to the US-dominated Human Genome Project. But by September 1999, the pure scientific character of the institute was lost at an inaugural meeting at Beijing Airport, which established the BGI as a company (officially renamed BGI in 2008).

**Early foundation in 1999**

The initial focus of the institution, however, seemed to be basic research. In 2002, BGI scientists completed the genomic sequence of rice (*Oryza sativa*) and were featured in a cover story in *Science* with these data (296, 79-92). In addition, the BGI disclosed the genome of the giant panda and the chicken (the latter published in *Nature*) – and attracted additional public attention in 2013 with an analysis on whether the genius of human beings can be found in their genes (*Nature* 497, 297–9). In Germany, the BGI came to prominence during the 2011 *E. coli* O104:H4 outbreak, with its fast identification of which *E. coli* strain was responsible for the uncommonly severe progression of EHEC infections.

According to their website, the Shenzhen-headquartered company’s mission is to work with genes from all living organisms and to modify their genetic code, and in common with almost every decent life science company around the globe, “to improve human health for the benefit of mankind.”

Sometimes, to BGI’s surprise, this benefit is not recognised by mankind. When, in 2015, for example, they put up mini-pigs for sale as pets, weighing no more than a cocker spaniel, the reaction was not as positive as they thought. The Chinese public was very critical of genetic modification due to some recent food scandals, involving the authorities, and people’s trust in biotechnology had suffered a backlash. Thus, genetically designed animals are no longer top of their agenda.

... offering low-priced sequencing

At about the same time, BGI began to place priority on offering low-price sequencing for scientists worldwide. With a huge workforce of several thousand, BGI expanded and is now a key player among USA’s Illumina, Agilent Technologies and Pacific Bioscience, Switzerland’s Roche and Germany’s Qiagen regarding next-generation sequencing. In line with this ambition, BGI bought Complete Genomics, located in California, in 2013, planning to exploit its technical know-how. Since then, BGI is no longer dependent on foreign companies for the construction of sequencing machines. They are now able to build them on their own.

BGI is now split into numerous companies. It’s nearly impossible to understand their company structure and entangled business relations, nor to understand if there is any difference between the two corporate names “BGI” and “BGI Genomics”, which have been used analogously for several years. For certain, the Chinese biotech showpiece’s core competence is next-generation sequencing as well as a broad portfolio of genetic tests, including prenatal screening, testing for hereditary cancer and rare diseases, as well as aiding precision medicine research (e.g. personalised...
therapy during cancer and preventing relapses is of high interest.

In the sequencing services business, as well as in research into genetically-based diseases and hereditary cancer, BGI (aka BGI Genomics) has long been the world-leader. It boasts a client network of about 10,000 organisations and 30,000 other partners, including services for 3,000 medical institutions and 300 hospitals, and collaborations with renowned companies like Qiagen, which provides software to BGI customers for the analysis of their sequencing results. Over half of their revenue was generated by prenatal testing and other reproductive health services, a market with enormous growth potential. In China alone, their non-invasive prenatal test reached sales of €243 million in 2016, with a prediction to reach €1.2 billion in 2020. The global genetic testing industry is on the way to become even bigger, with a total expected market of €9.2 billion in 2018.

BGI now operates in more than 100 countries. But this expansion is not accompanied by universal applause. This year, another BGI company, iCarbonX, is investing more than €100 million in US-based social networking service, PatientsLikeMe. iCarbonX is a pioneer in artificial intelligence (AI) software, programmed to recognise useful relationships between large volumes of biological, medical, behavioural and psychological data relating to a single individual. Thus, it makes sense for a genomics analysis company like BGI, to be interested in PatientsLikeMe, the biggest online network of patients with rare and chronic disease.

National security threatened?

But at the same time, several US institutions are alarmed. In China, industry relies on cloud computing and iCarbonX offers their customers a smartphone app, Meum, to consult for health advice. Clouds and security is an issue on its own. One thinks, for example, of the frequently-hacked private pictures of Hollywood stars. Personal data regarding health and intimacy, however, is far more concerning than trivial nude photos.

Some, however, even see a threat to national security. Take Eleonore Pauwels, Director of Biology Collectives at Wilson Centre in Washington, DC, who recently warned in an interview published by thediplomat.com that, "using AI systems to understand how the functioning of our genom-es impacts our health is of strategic importance for biodefence. This knowledge will lead to increasing developments at the forefront of medical countermeasures, includ-

ing vaccines, antibiotics, and target treatments relying on virus-engineering and microbiome research."

Again, one is tempted to bring Hollywood to the table, this time as a storyboard for a scientific thriller.

Exceptional funding by the government

Besides science fiction, this sounds a lot like scientific Big Data. A fitting piece to the puzzle might be the establishment of the China National GeneBank in Shenzhen (also the location of BGI’s headquarters), in alliance with the Chinese government.

In 2010, it was reported that the Chinese Development Bank will provide BGI with an equivalent of about €1.3 billion in collaborated funds over ten years. In this regard, last year’s BGI revenues of about €210 million sounds like peanuts.

Nevertheless, the company went public in July this year. Initially, BGI announced plans to raise an equivalent of €218 million. However, this huge stock offering would have required a special risk note. Therefore, BGI decided to aim for only €70 million in their IPO. Today, two months later, BGI stock has exploded by nearly 700 percent, compared with its first-day price. Well, many people seem to believe in the power (right lion) and the prosperity (left lion) of BGI. But the question is: Why did the company go public at all? Normally, a company decides to go public because it needs money for investments. The BGI group, however, already has sufficient capital. Maybe, they wanted to send a signal to their competitors worldwide: “We are strong and alive, hungry and biting – take note of this and stay away from our business.”

Next rookie’s IPO

This signal is not being sent only by BGI. Domestic rivals are also using it. For example, another Chinese biotech rookie, Berry Genomics, founded in 2010 by a team of former BGI executives. The company performed several successful rounds of fundraising, including the engagement of Legend Capital, probably better known for the brand Lenovo, with a total investment of over €100 million.

The Berry Genomics portfolio includes prenatal genetic testing, DNA sequencing, and other forms of genetic testing for disease screening and diagnosis. A rogue, not thinking of BGI interests. One month after BGI, Berry Genomics went public in August 2017, through the back door, performing a reverse merger with Shenzhen-listed Chengdu Tianxing Instrument & Meter, valuing Berry Genomics at €518 million.

Chengdu Tianxing traditionally produces components for the automobile and motorcycle industry and is selling now, after the reverse merger, speedometers as well as prenatal genetic diagnostic tests.

So, the Chinese biotech lion is hungry for a bigger market share and it will bite. On the other hand, the rest of the world still has time and shouldn’t be too alarmed. Try a quick Google search for Berry Genomics! The first hit allays suspicions that Berry intends to operate internationally in the near future:

Thorsten Lieke
Germany’s Immunic Therapeutics pockets €32 million

Cash Infusion

Biotech euphoria in Southern Germany?
Immunic Therapeutics, drug development newcomer, has convinced international investors.

Is there a new star rising in the German biotech sky? Venture capital investors obviously believe glowingly in the research programme of the clinical stage biotech company, Immunic Therapeutics (located at Germany’s main biotech hub, Martinsried, see picture above). They have showered the start-up with a whopping overall investment of nearly €32 million. Immunic closed its series A financing round in September 2017, about one year after it started in late 2016. The final shareholder syndicate includes Omega Funds (Boston, USA), Fund+ (Leuven, Belgium), LSP Life Sciences Partners (Amsterdam, The Netherlands), LifeCare Partners (Basel, Switzerland) and some German venture capitalists.

Old hands in the business
€32 million is an exorbitant amount, at least by German biotech standards. Where does this trust in the Bavarian start-up come from?

Although Immunic Therapeutics was founded as late as April 2016, the managing team members are no unknowns in the pharmaceutical industry. Immunic’s CEO, Daniel Vitt, started his industry career in 1997, co-founding neighbouring 4SC, a biotech company developing small-molecule drugs. After some teething problems, 4SC grew from a small research start-up to a large company, entering the Frankfurt stock exchange in 2005. In May 2017, share values nearly doubled after 4SC announced a new financing round to push its lead candidate, Resminostat, an epigenetic cancer therapy, into market approval.

In 2016, however, 4SC decided to focus on oncology therapeutics, and that’s when Vitt left, together with Manfred Gőppel (now Immunic’s COO) and Hella Kohlhofer (now CSO), to found Immunic Therapeutics. This concentrated management experience together with Immunic’s two immune-modulating drugs, IMU-838 and IMU-336, which incidentally were both outsourced from 4SC, might have been convincing enough for investors to provide a lot of money. The two small molecule drugs will, it is hoped, cure autoimmune and inflammatory bowel diseases.

Targeting the immune system
Crohn’s disease as well as ulcerative colitis affect the gastrointestinal tract. Severe inflammations lead to abdominal pain, diarrhoea and anaemia. In western industrialised countries, approximately 0.4% of the citizens suffer from these chronic diseases, triggered by an overactive immune system accompanied with excessive T cell activity induced by T helper cell cytokine release.

Lead drug candidate IMU-838 is an orally available inhibitor molecule, targeting dihydroorotase dehydrogenase (DHODH). This enzyme catalyses one step in the pyrimidine biosynthesis. By inhibiting DHODH, IMU-838 decreases the de novo synthesis of pyrimidine and thereby limits the proliferation of activated lymphocytes and the release of cytokines by T helper cells. Thus, an exuberant immune response can be avoided or regulated.

There are already DHODH inhibitors commercially available, for example the immunomodulatory drugs Leflunomide (brand name Arava) and Teriflunomide (brand name Aubagio) from Sanofi (Paris, France), approved for rheumatoid and psoriatic arthritis. Clinical studies for other chronic inflammatory or autoimmune diseases, like multiple sclerosis and Crohn’s disease, are still ongoing.

So, Immunic Therapeutics is urging for tests on IMU-838 in a phase II study in patients with ulcerative colitis and Crohn’s disease, in early 2018. With the convenient financial nest egg of €32 million, these plans are becoming ever more concrete.

The second drug candidate in Immunic’s pipeline is IMU-366, still in pre-clinical development for psoriasis. Psoriasis patients suffer from itchy, scaly patches covering their skin, resulting from abnormally rapid growth of the epidermis. Like in other autoimmune diseases, an exuberant immune response triggered by T helper cells is thought to play a key role in these chronic inflammatory alterations. Retinoic acid-related orphan receptor γt (RORγt), a nuclear receptor transcription factor, is known to regulate the development of a helper T cell subset (Th17) and by this, the production of a wide range of cytokines. By inhibiting RORγt with the orally administered IMU-366, Immunic hopes to silence T helper cell-mediated inflammatory symptoms in psoriasis.

Strong competition
Also other RORγt inhibitors are under development for the treatment of chronic inflammations and autoimmune diseases, like rheumatoid arthritis, for instance. US biopharmaceutical company Lycera (Ann Arbor, Michigan) provides two RORγt agonists: pre-clinical LYC-56056, targeting autoimmune diseases, and LYC-55716, which is already in phase I studies to prove its effect on solid tumours. Additionally, Lycera’s lead drug candidate LYC-30937, an ATPase modulator, is being studied in clinical phase II to treat ulcerative colitis and psoriasis.

In light of strong competitors like Lycera, there are enough reasons for Immunic Therapeutics to get a move on in their research and squeeze the best possible results out of their fresh capital. Sigrid März
Patent case against Teva: Synthon wins

David defeats Goliath

Bible stories are entertaining, but they usually lack reality. In this case, however, the biblical legend was caught up in the real world: A rather small generic drugmaker defeats a much larger one in court.

There are nicer activities than provoking one of the world’s largest pharmaceutical companies. But what if they restrict your company’s operational manoeuvrability with patent-related claims? If this happens, you will be forced to agree, or to disagree and prepare yourself for years of fierce and expensive litigation.

Plucky Synthon, a mid-size pharmaceutical company from Nijmegen, The Netherlands, did the latter when all-powerful generic drug manufacturing Goliath, Teva Pharmaceuticals (headquartered in Petah Tikva, Israel), sent a warning letter in 2015. It was about a multiple sclerosis (MS) drug, which has been marketed by Teva under the brand name Copaxone since 1997 – and which Synthon intended to market as a less expensive, generic version, too.

A former MS blockbuster

Copaxone (or glatiramer acetate, see inset photo) is a synthetic analogue of myelin basic protein, which is presumably involved in the pathogenesis of MS. Its therapeutic effects are thought to act via immunomodulation and neuroprotection.

However, the patent on glatiramer acetate expired in 2015, with the result that competitors, as of that date, were allowed to market the drug themselves. Synthon and others, like Novartis subsidiary Sandoz, immediately seized the opportunity to earn money without having invested in previous development, whilst Teva lost no time in taking countermeasures. The Israelis instantly developed a longer-lasting formulation of Copaxone, which reduces the formerly once-daily treatment to a three-times-a-week administration. At the same time, they applied – and obtained – US patent protection for those new, long-acting delivery formulations.

The “refreshing patents” strategy

Exactly this is the sticking point in this case. Teva’s opponents, such as Novartis and Synthon, complain that those newer patents are invalid. If they were upheld, any marketing of rival, long-acting generics of a 20-year-old drug would be prevented, they argue. Teva’s strategy of “refreshing” their expired Copaxone patents by coming up with new formulations or slightly modified mixtures is referred to in the pharmaceutical industry as “evergreening”, a disputed but often-used practise to restrict or prevent competition.

They complained successfully. Teva’s long-acting delivery patents were scuppered and litigation against the Israeli was quick to shatter four of their five new patents. By the time this issue of Lab Times went to print on 20th September, the Technical Board of Appeal (TBA) of the European Patent Office (EPO) had also revoked the last of Teva’s glatiramer so-called HBr patents, “for an improved process for the synthesis of glatiramer acetate”.

According to Synthon, the TBA’s decision, “confirms that [Teva’s legal] actions lacked legal basis and thus were unjustified”. As a consequence, Teva’s competitors now have a green light to approve and market their own generic versions of Copaxone (alias glatiramer acetate). Synthon, for example, has performed a large-scale phase III study for their own glatiramer acetate generic drug and is now busy obtaining marketing authorisations for it in most European countries. This time, at least, “David” Synthon (with a turnover of €258 million in 2016, generated by 1,900 staffers) has defeated “Goliath” Teva (€17.7 billion; 57,000 employees).

Winfried Koeppelle

Regarding glatiramer acetate (small photo), “David” Synthon had to defend against “Goliath” Teva – and won.
Abivax confirms spectacular clinical data on HIV reducing drug

Disclosed, reduced... – but not defeated

Can the HIV virus be completely eradicated from the body? A French biotech company is spreading hope, but even if the latest study results appear spectacular, most experts remain sceptical.

AIDS has been defeated several times. Take the case of Timothy Ray Brown, better known as “The Berlin Patient”. Brown, who was diagnosed with HIV in 1995, underwent a stem cell transplantation to treat leukaemia in 2007. Since then, researchers haven’t been able to detect any HIV viruses in Brown’s blood or in biopsies, and even the levels of HIV-specific antibodies in his body have declined. This apparently complete cure of HIV/AIDS was probably due to the uncommon kind of bone marrow stem cells Brown received, carrying the homozygous [CCR5]-∆32 receptor mutation and thus blocking the attachment of HIV to their surface. Others speculate that the healing effect (i.e. eradication of the HIV-infected cells) could also have been due to the graft-versus-host disease that Brown suffered one year after his transplant. Apart from the fact that Brown’s miracle cure is not yet completely understood, his special case shouldn’t be taken as a blueprint for the treatment of HIV patients. Nevertheless, increasingly we hear news of cases in which patients were allegedly cured of AIDS. In July 2016, leading Australian scientists and representatives of official organisations even published a statement that AIDS is, “virtually eliminated” in their country and therefore no longer a threatening epidemic for the public. Modern drugs can prevent infection with the HIV virus (HIV), and the few patients with AIDS-related symptoms are treated with drugs.

It was in July this year, during the 9th IAS Conference on HIV Science (IAS 2017), when a South African paediatrician presented the stunning newest case of “healing HIV/AIDS”. It was about a nine-year-old Johannesburg child, who had been infected with HIV at birth by his mother. Treated immediately with antiretroviral drugs for just 40 weeks, no active HIV viruses have since been found in the child’s body.

Just asleep, not gone

However, there are still “sleeping” viral residues present in her body after nine years, hiding in long-lived infected T cells, which could lead to a new infection some day. The identification and eradication of these hidden HIV reservoirs (often located in peripheral blood mononuclear cells, PBMCs) has long been at the top of researchers’ wish lists. The challenge in doing this is the sheer number of body cells in every living person: The few infected cells must be destroyed completely, without exception, but the remaining billions shouldn’t be killed or even damaged by the therapy.

Some HIV viruses hide in long-lived infected T cells and thus evade virus detection for years. Like this cute crocodile, they are very hard to find, study and kill.
In March 2017, collaborating scientists from Montpellier and Paris published new insights about ways of detecting and selectively destroying those reservoirs (Nature 543, 564-8). The French had found a specific gene expression signature of 103 upregulated genes that are specific for latently HIV-1 infected cells, and selected the low-affinity receptor for the IgG Fc fragment, CD32a, as the most promising target to track down lymphocytes that host copies of HIV DNA.

With 37 million HIV infected people worldwide, of whom 17 million are treated, the industry is also keen to take part in this race. Paris-based Abivax is one of the forerunners when it comes to identifying dormant HIV infected cells. Their ABX464 compound is an orally available small molecule that blocks HIV replication. Unlike the current gold standard in HIV treatment, antiretroviral therapy (ART), ABX464 could completely eliminate the virus and prevent it from coming back after treatment is halted.

Encouraging or meaningless results?

In May 2017, Abivax announced the preliminary results of a phase IIa trial in 22 HIV patients who were treated with ART plus ABX464 for four weeks (plus 8 patients who received a placebo). Thereafter treatments were stopped to observe whether and how strongly the virus returned.

The results were both encouraging but also a bit meaningless. On the one hand, only the data from 14 participants who were treated with ART/ABX464 could be evaluated. That number is far too small, of course, to be able to state anything substantial. On the other hand, in 7 of those patients, a significant reduction of viral HIV DNA was observed, “We saw an average decrease of 40% of the reservoir”, Jean-Marc Steens, CMO of Abivax, told the press, adding that, “it’s the first time that a pharmacological agent has proved to be able to reduce the reservoir in HIV patients”.

But why didn’t the other participants respond to the new therapy? Were they treated in different ways to their fellow sufferers before the ABX464 trial started? Or were they in a different disease state? At the moment, Abivax is conducting another phase IIa trial. After a subsequent phase Ib trial in a larger number of patients, the moment of truth will come, with the ultimate phase III study by the end of 2018 or early 2019.

Enthusiasm on the stock market

At the stock exchange, however, there was no reason for prudence. Immediately after Abivax announced their phase II results of limited relevance, the stock price exploded by 176 percent. Meanwhile, its share price has fallen somewhat, but is still twice as high as before the relevant press release.

Winfried Koeppelle
Product survey: Gel documentation systems

Digitising Gels

CCD camera-based gel imagers offer a whole bunch of illumination options and are about to enter the last territories ruled by laser scanners, such as the analysis of 2D differential gels.

C apturing gels on pictures with gel documentation (gel doc) systems is routine in many life science labs. In the old days (not entirely sure they were always the good old days) of biochemistry and molecular biology, gel documentation was mostly done with the legendary GelCam. Simple enough, the GelCam was basically a Polaroid camera mounted on a hood that served as a small portable darkroom. The hood was imposed over the gel lying on the glass plate of a transilluminator desk and, after pulling the trigger of the GelCam, an instant black and white photo was pulled out of the camera, showing the protein or DNA bands on the gel.

The cool thing about the GelCam was its simplicity and also its honesty: the gel picture was glued into the lab book without any further image “manipulation”. But the Polaroids only allowed a qualitative estimation of the protein or DNA bands on the gel.

Aficionados of vintage cameras and Polaroid photos may still get hold of used GelCams on eBay or lab equipment auctions on the internet. But it’s way easier to buy a digital version of the GelCam with a modern, scientific grade, digital camera instead of the old analogue Polaroid camera. The simplest models don’t even have a fixed scientific-camera on top of the hood. Instead, popular smartphones may be mounted above the platform to capture the gel images.

Digital GelCam offsprings

More sophisticated digital offsprings of the GelCam are already equipped, for example, with 12-bit CCD cameras, providing a native resolution of about one or two megapixel and an image depth (gradation) of 4,096 (212) shades of grey. They usually come with exchangeable emission filters to document, for example, ethidium bromide or SYBR green-stained gels. Included entry-level imaging software packages, running on an external PC, allow visualisation and documentation of gels as well as basic quantifications of stained protein or nucleic acid bands. If you need more illumination options, higher resolution, more grey shades and powerful band quantification software, you should take a closer look at bench top systems. Their basic set-up is pretty much the same for all models, though the design may slightly vary between different manufacturers: the gels are placed on a drawer that slides out of the built-in darkroom after opening a small door. A transilluminator with two or three different UV tubes is integrated in the drawer to illuminate, for example, ethidium bromide or SYBR gold-stained gels. The UV table may be adapted with conversion screens for transmission of white or blue light to detect Coomassie-stained gels or safe fluorescent dyes, respectively. Additional multi-coloured LEDs or epi white lights and blue LEDs installed above the drawer, at the side of the darkroom, enable fluorescence imaging and overhead white and blue light imaging.

Cooled cameras

Higher priced, stand-alone instruments, with a built-in computer system and touch-screen-controlled imaging software, usually provide even more illumination features, such as accessory infrared laser diodes. They may be configured with different cooled 16-bit CCD cameras, providing up to 65,536 grey levels and nine or even more megapixel resolution.

Gel doc systems with high-resolution CCD cameras already rival laser scanner-based systems in the analysis of 2D differential gels (2D-DIGE). In 2D-DIGE experiments, two protein probes (e.g. disease and control) as well as an internal standard are labelled with different fluorescence dyes and separated through isoelectric focusing and PAGE. Since all probes are loaded on a single gel, variations between two different gel runs, are eliminated. Due to the internal standard and the sensitive fluorescence label, 2D-DIGE indicates even slight variations in the expression of differently labelled proteins.

The analysis of 2D-DIGE gels usually requires a very expensive laser scanner system that reads the gel point-by-point and converts the emitted light signals into an accurate gel image. The scanning process is pretty slow and takes, for example, about half an hour for a 21 x 27 centimetre-sized gel. And you should also have ample storage capacities on your PC, since the gel data set requires about 12 MB storage space.

Challenging the top dog

But recent progress in LED illumination and CCD camera resolution enables CCD-based gel doc systems to compete with laser-based systems in analysis of 2D-DIGE gels. Ralf Rabus’ group at the University of Oldenburg, Germany, compared the performance of GE’s Typhoon 9400 laser scanner, which is the benchmark instrument in 2D-DIGE imaging, with a new CCD-based 2D-DIGE imager developed by the German company Intas (Proteomics 16, 1975-79). The team prepared protein extracts from various environmental bacteria strains, separated the proteins on 2D-DIGE gels and digitalised replicate gels with the Typhoon and the 16-bit CCD imager. The latter utilises fluorescence dye-specific LED arrays, arranged on both sides of the darkroom at an optimised angle to evenly illuminate the complete 2D-DIGE gel area.

It is no surprise that the CCD imager operated at a much faster speed (three minutes to capture a 21 x 27 cm gel) than the Typhoon and required less storage space (3.8 MB per image). But there was also no significant difference in the number of spots that both systems detected. The camera-based system identified only slightly less spots than the laser scanner and “recovered between 86 to 90% of the protein spots detected in images acquired by the laser scanner”. The average ratio numbers, which are the true biological relevant numbers indicating statistically significant changes in protein levels of probes and controls, were, however, very similar for both systems.

It seems that CCD gel doc systems are just about to conquer one of the last strongholds of laser-based systems.

Harald Zähringer
## Gel Documentation Systems

<table>
<thead>
<tr>
<th>Company/Distributor</th>
<th>Name of Product</th>
<th>Light sources</th>
<th>Image resolution</th>
<th>Miscellaneous, Specialities, Generally</th>
<th>Price [EUR]</th>
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</thead>
<tbody>
<tr>
<td><strong>AlphaMetrix Biotech</strong>&lt;br&gt;Roedermark, Germany&lt;br&gt;www.alphametrix.de&lt;br&gt;Contact: Heiner Sanders&lt;br&gt;Phone: +49 60742116240&lt;br&gt;<a href="mailto:syngene@alphametrix.de">syngene@alphametrix.de</a></td>
<td>G:Box Mini (New)</td>
<td>Transilluminator UV / Blue LED, white light, HI-LEDs red/green/blue</td>
<td>6 or 9 MP camera</td>
<td>Stain-free imaging</td>
<td>Approx. 17,000.–</td>
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<td></td>
<td>NuGenius</td>
<td>Epi white light</td>
<td>5 MP camera, 0.4 inch sensor</td>
<td>Fluorescence</td>
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<td>12/16-bit</td>
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<td>Approx. 14,000.–</td>
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<td>G:Box Chemi XRQ</td>
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<td>Chemiluminescence</td>
<td>Approx. 18,000.–</td>
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<td>Chemiluminescence, fluorescence, coloured fluorescent, multiplex and colorimetric imaging</td>
<td>Approx. 21,000.–</td>
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<td>G:Box Chemi XX6</td>
<td>Epi white light</td>
<td>6 MP imaging 16-bit camera/9 MP imaging 16-bit camera with 73% QE @ 425 nm, cooled -57°C</td>
<td>Chemiluminescence, fluorescence, coloured fluorescent, multiplex and colorimetric imaging</td>
<td>Approx. 23,000.–</td>
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<td>G:Box Chemi XX9</td>
<td>Epi white light</td>
<td>4 MP imaging 16-bit camera with 73% QE @ 425 nm with fixed 0.9 lens</td>
<td>Chemiluminescence</td>
<td>From 10,200.–</td>
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<td></td>
<td>GeneGnome XRQ</td>
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<td>9 MP camera</td>
<td>Chemiluminescence</td>
<td>From 12,000.–</td>
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<td>Effective pixels: 24.98 MP</td>
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<td>Fixed lens: f1.4</td>
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<td>Max. viewing area: 13 x 10 cm</td>
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<tr>
<td><strong>Analytik Jena</strong>&lt;br&gt;Jena, Germany&lt;br&gt;www.bio.analytik-jena.com&lt;br&gt;Contact: Phone +49 36 41 7770&lt;br&gt;<a href="mailto:lifescience@analytik-jena.com">lifescience@analytik-jena.com</a></td>
<td>UVP GelStudio Plus</td>
<td>Epi-white LED light</td>
<td>5.0 MP resolution</td>
<td>Light-sensitive monochrome camera with motorised high quality zoom lens</td>
<td>10,200.–</td>
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<td></td>
<td></td>
<td>Thin-line UV transilluminator (standard)</td>
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<td>Streamlined software interface</td>
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<td>(optional): overhead UV and eETE source, blue and white transilluminators</td>
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<td>&quot;Slide-away&quot; front door</td>
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<td></td>
<td>UVP GelStudio Plus touch</td>
<td>See above</td>
<td>5.0 MP resolution</td>
<td>Light-sensitive monochrome camera with motorised high quality zoom lens</td>
<td>11,490.–</td>
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<td>Streamlined software interface for image acquisition</td>
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<td></td>
<td>UVP GelTower</td>
<td>Overhead white LED light, interchange-able transilluminations sources: white, blue, midrange and long-wave UV</td>
<td>17.9 MP resolution</td>
<td>Colour or grayscale publication-quality images</td>
<td>6,900.–</td>
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<td>5-position filter wheel</td>
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<td>Simple workflow-focused software</td>
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<td>Smaller than 33 cm x 33 cm footprint</td>
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<td></td>
<td>UVP UV Solo touch</td>
<td>Overhead white LED light</td>
<td>5.0 MP resolution</td>
<td>Touch screen operation</td>
<td>7,290.–</td>
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<td>Light-sensitive monochrome camera</td>
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<td>Maximum UV protection</td>
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<td>Easy-access filter drawer</td>
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<td>Small footprint</td>
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<tr>
<td><strong>Bio-Rad Laboratories</strong>&lt;br&gt;Muenchen, Germany&lt;br&gt;www.bio-rad.com&lt;br&gt;Contact: Phone +49 89 31884 177&lt;br&gt;<a href="mailto:info.sales.LSG@bio-rad.com">info.sales.LSG@bio-rad.com</a></td>
<td>Gel Doc EZ</td>
<td>Trans UV, white light, blue light</td>
<td>12-bit system (~1.4 MP)</td>
<td>Automatic tray detection</td>
<td>Current special price of starting at, 4,469.25</td>
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<td>Dynamic image resolution &gt; 4 MP</td>
<td>Optimised for small and medium format gels</td>
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<tr>
<td></td>
<td>Gel Doc XR+</td>
<td>UV trans illumination with an optional white or blue light conversion</td>
<td>12-bit system (~1.4 MP)</td>
<td>For small and large format gels</td>
<td>Current special price of starting at, 7,133.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dynamic image resolution &gt; 4 MP</td>
<td>Upgradeable for chemiluminescence detection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unlimited licensed Image Lab software</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChemiDoc XRS+</td>
<td>See above</td>
<td>16-bit system</td>
<td>For small and large format gels and blots</td>
<td>Current special price of starting at, 12,967.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dynamic image resolution &gt; 4 MP</td>
<td>Sensitive chemiluminescence detection</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Unlimited licensed Image Lab software</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stain-free compatibility for image capturing and analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preparative work- ing with standard distribution package possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChemiDoc MP</td>
<td>Trans UV, 302 nm excitation</td>
<td>16-bit system</td>
<td>Touch screen operated system</td>
<td>On request</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epi white, Trans (white, blue), Epi (blue, green, red, far red, near IR on request)</td>
<td>Multiplex fluorescent western blotting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Filters to perform protein and DNA gel and blot imaging</td>
<td>Automatic selection of optimal light source</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stain-free protein normalisation</td>
<td>Three sample trays cover diverse imaging applications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16-bit system</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>~4 orders of magnitude</td>
<td></td>
</tr>
<tr>
<td>Company/Distributor</td>
<td>Name of Product</td>
<td>Light sources</td>
<td>Image resolution</td>
<td>Miscellaneous, Specialities, Generally</td>
<td>Price (EUR)</td>
</tr>
<tr>
<td>---------------------</td>
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<td>---------------</td>
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</tr>
<tr>
<td>Bio-Rad Laboratories (continued)</td>
<td>ChemiDoc</td>
<td>Trans UV, 302 nm excitation, Trans white/blue</td>
<td>16-bit system</td>
<td>Dynamic image resolution &gt; 4 MP</td>
<td>Touch-screen operated system</td>
</tr>
<tr>
<td></td>
<td>GS-900 Calibrated Densitometer</td>
<td>16-bit scanner with a large dynamic range (up to 4.3 OD)</td>
<td>16-bit precision and 36.5 µm</td>
<td>Transmissive and reflective imaging using red, green and blue CCD technology</td>
<td>Starting at 13,105.–</td>
</tr>
<tr>
<td>Bio-Budget Technologies</td>
<td>Doc-Print VX5</td>
<td>Without UV table (light protection hood with 23 x 27.5 cm tubing opening)</td>
<td>Scientific grade CCD camera with b/w-sensor (16-bit, 65,536 grey shades, 2 MP)</td>
<td>No computer necessary</td>
<td>On request</td>
</tr>
<tr>
<td></td>
<td>DNA Gel</td>
<td>UV transilluminator</td>
<td>-25°C cooled CCD camera</td>
<td>Grey scales: 1,390 x 1,040, 16-bit</td>
<td>8” touch screen, Mini-PC</td>
</tr>
<tr>
<td></td>
<td>Chemiluminescence Gel</td>
<td>UV transilluminator</td>
<td>-25°C cooled CCD camera</td>
<td>Grey scales: 1,390 x 1,040, 16-bit</td>
<td>8” touch screen, Mini-PC</td>
</tr>
<tr>
<td></td>
<td>Chemiluminescence &amp; DNA Gel</td>
<td>UV transilluminator</td>
<td>-25°C cooled CCD camera</td>
<td>Grey scales: 1,390 x 1,040, 16-bit</td>
<td>8” touch screen, Mini-PC</td>
</tr>
<tr>
<td>Bioolympics/Royal Biotech</td>
<td>Digital Gel</td>
<td>UV transilluminator</td>
<td>49K2 white light</td>
<td>2 MP resolution, extendable to 7.6 MP, 16-bit, 65,536 grey levels</td>
<td>Software-controlled illumination</td>
</tr>
<tr>
<td></td>
<td>UV Transilluminator</td>
<td>Ultra bright 15 X 6 tube</td>
<td>--</td>
<td>306 or 254/365 nm</td>
<td>On request</td>
</tr>
<tr>
<td></td>
<td>UV Transilluminator</td>
<td>Ultra bright 15 X 6 tube</td>
<td>--</td>
<td>306 or 254/365 nm</td>
<td>On request</td>
</tr>
<tr>
<td>Biostep</td>
<td>PC-controlled systems</td>
<td>White light (transmission and overhead)</td>
<td>Digital 18 MP reflex camera</td>
<td>Modular system</td>
<td>From 2,945.–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Felix: 1010 / 2010</td>
<td></td>
<td>PC control of camera, hood, transilluminator and light sources</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1020 / 2020</td>
<td></td>
<td>Integrated data bank for image storage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1030 / 2030</td>
<td></td>
<td>Imaging software</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1040 / 2040</td>
<td></td>
<td>Direct printer and USB stick</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1050 / 2050</td>
<td></td>
<td>Data bank for image storage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stand-alone systems:</td>
<td>White LED overhead and transmission, UV transmission</td>
<td>12-bit CCD camera</td>
<td>Stand-alone system</td>
<td>From 3,450.–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gerik 1000, 1010, 1020, 1030, 1040, 1050</td>
<td></td>
<td>Automated control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gel-Scanner:</td>
<td>Overhead illumination and transillumination</td>
<td>Max. 5.29 µm, 16-bit grey scales, 48-bit colour</td>
<td>Direct, method-based scanner control</td>
<td>From 1,565.–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ViewPix 700, 900, 1100, 1300</td>
<td></td>
<td>GLP/GMP conformity, calibration up to 3.8 OD</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transmission and reflexion mode</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Colour channel optimisation</td>
<td></td>
</tr>
<tr>
<td>Biozym Scientific</td>
<td>FlashGel System</td>
<td>Blue light LEDs</td>
<td>Digital/C莫斯 camera</td>
<td>Real-time separation and documentation in 5 min</td>
<td>From 1,224.–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,280 x 960 pixel</td>
<td>Five to twenty times more sensitive than EtBr; detection limit for DNA &lt; 0.1 ng and for total RNA &lt; 10 ng</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c150 / c200</td>
<td>Dual wavelength UV transilluminator</td>
<td>5.4 MP</td>
<td>16-bit image output</td>
<td>Upgradeable system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epic blue LEDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conversion screen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>c300</td>
<td>Dual wavelength UV transilluminator</td>
<td>25°C cooled CCD camera</td>
<td>8.3 MP CCD camera, cooled and regulated, 50 °C below ambient</td>
<td>Upgradeable system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epic blue LEDs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Conversion screen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>c600</td>
<td>Laser diodes (660 nm, 785 nm) RGB LEDs</td>
<td>25°C cooled CCD camera</td>
<td>8.3 MP CCD camera, cooled and regulated, 50 °C below ambient</td>
<td>Gei and Western Blotting imaging system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual wavelength UV transilluminator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epic blue LEDs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Gel Documentation Systems

<table>
<thead>
<tr>
<th>Company/Distributor</th>
<th>Name of Product</th>
<th>Light sources</th>
<th>Image resolution</th>
<th>Miscellaneous, Specialities, Generally</th>
<th>Price [EUR]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corning Incorporated</strong>&lt;br&gt;Life Sciences Europe&lt;br&gt;Amsterdam, Netherlands&lt;br&gt;Contact: Phone +31 20 659 6051&lt;br&gt;CSEuro incentcom.com</td>
<td>Axygen&lt;br&gt;(302 &amp; 365 nm), blue light&lt;br&gt;(470 nm, optional), white light (transmission option)</td>
<td>5.4 MP camera, 16-bit TIFF files</td>
<td>Optional image analysis and quantification of bands</td>
<td>4,850.– to 7,950.–</td>
<td></td>
</tr>
<tr>
<td><strong>GE Healthcare</strong>&lt;br&gt;www3.gehealthcare.de&lt;br&gt;Contact: <a href="mailto:ordersde@ge.com">ordersde@ge.com</a></td>
<td>ImageQuant LAS 500&lt;br&gt;Epi (UV, blue, white)</td>
<td>Peltier-cooled, 8.3 MP CCD camera</td>
<td>30 x 28 cm footprint</td>
<td>On request</td>
<td></td>
</tr>
<tr>
<td><strong>Herolab Laborgeräte</strong>&lt;br&gt;Wiesloch, Germany&lt;br&gt;Contact: Iris Sauer&lt;br&gt;Phone +49 62 22 5802 15&lt;br&gt;<a href="mailto:iris.sauer@herolab.de">iris.sauer@herolab.de</a></td>
<td>ChemaLum 8300&lt;br&gt;Various transilluminators or Epi light modules</td>
<td>Cooled 8.3 MP scientific grade CCD camera, 16-bit</td>
<td>Multi-imaging system for chemiluminescence and multiples fluorescence, high sensitivity</td>
<td>From 22,000.–</td>
<td></td>
</tr>
<tr>
<td><strong>Intas</strong>&lt;br&gt;Goettingen, Germany&lt;br&gt;Contact: Phone: +49 551 50 50 50&lt;br&gt;<a href="mailto:info@intas.de">info@intas.de</a></td>
<td>E.A.S.Y Doc plus&lt;br&gt;(UV transilluminator)</td>
<td>1.4 MP scientific grade CCD camera, 16-bit</td>
<td>Easy handling, for gel sizes 22 x 28 cm, moveable drawer, high resolution</td>
<td>From 6,300.–</td>
<td></td>
</tr>
<tr>
<td><strong>Herolab Laborgeräte</strong>&lt;br&gt;Wiesloch, Germany&lt;br&gt;Contact: Iris Sauer&lt;br&gt;Phone +49 62 22 5802 15&lt;br&gt;<a href="mailto:iris.sauer@herolab.de">iris.sauer@herolab.de</a></td>
<td>MiniDoc plus&lt;br&gt;LED blue or white light or UV transilluminator</td>
<td>1.4 MP scientific grade CCD camera, 16-bit</td>
<td>Small size, easy handling, for gel sizes 14 x 22 cm, moveable drawer, good resolution</td>
<td>From 4,800.–</td>
<td></td>
</tr>
<tr>
<td><strong>Intas</strong>&lt;br&gt;Goettingen, Germany&lt;br&gt;Contact: Phone: +49 551 50 50 50&lt;br&gt;<a href="mailto:info@intas.de">info@intas.de</a></td>
<td>HeroDoc plus&lt;br&gt;(Integrated UV transilluminator)</td>
<td>1.4 MP scientific grade CCD camera, 16-bit</td>
<td>Motorized aperture and focus</td>
<td>From 7,900.–</td>
<td></td>
</tr>
<tr>
<td><strong>Li-Cor Biosciences</strong>&lt;br&gt;Cambridge, UK&lt;br&gt;www.li-corp.com&lt;br&gt;Contact: Phone +44 1223 422104&lt;br&gt;<a href="mailto:bio-eu@li-corp.com">bio-eu@li-corp.com</a></td>
<td>D-Digit Gel Scanner&lt;br&gt;Blue LED</td>
<td>130, 300, 600 dpi</td>
<td>Sensitive safe stain imaging of nucleic acid gels</td>
<td>3,490.–</td>
<td></td>
</tr>
<tr>
<td><strong>LTF Labortechnik</strong>&lt;br&gt;Wasserburg, Germany&lt;br&gt;Contact: Noel Kändler&lt;br&gt;Phone +49 8382 98 520&lt;br&gt;<a href="mailto:info@labortechnik.com">info@labortechnik.com</a></td>
<td>Römerm Diversity 200 / 500 / 700&lt;br&gt;UV, white light, incident light</td>
<td>Diversity USB camera, based on Sony ICX CCD sensor with 16-bit pixel depth and 1.4 MP sensor resolution</td>
<td>Filter wheel with 6 positions</td>
<td>On request</td>
<td></td>
</tr>
<tr>
<td><strong>LTF Labortechnik</strong>&lt;br&gt;Wasserburg, Germany&lt;br&gt;Contact: Noel Kändler&lt;br&gt;Phone +49 8382 98 520&lt;br&gt;<a href="mailto:info@labortechnik.com">info@labortechnik.com</a></td>
<td>Syngene NuGenius / NuGenius+&lt;br&gt;White light, blue light, UV&lt;br&gt;UV white light converter screen and UV blue light converter screen</td>
<td>5 MP camera, bit depth: 12/16-bit, 0-65,536 grey scales, dynamic range 3.6/4.8 (extended), lens manually or motor-driven 6.5–39, f/1.4</td>
<td>Touch screen</td>
<td>On request</td>
<td></td>
</tr>
<tr>
<td><strong>LTF Labortechnik</strong>&lt;br&gt;Wasserburg, Germany&lt;br&gt;Contact: Noel Kändler&lt;br&gt;Phone +49 8382 98 520&lt;br&gt;<a href="mailto:info@labortechnik.com">info@labortechnik.com</a></td>
<td>Syngene GeneGnome XRQ&lt;br&gt;LED incident light</td>
<td>CCD camera with 4 MP, cooling regulated -5°C, A/D&lt;br&gt;16-bit</td>
<td>Fully-automated system especially for Western Blots</td>
<td>On request</td>
<td></td>
</tr>
<tr>
<td><strong>LTF Labortechnik</strong>&lt;br&gt;Wasserburg, Germany&lt;br&gt;Contact: Noel Kändler&lt;br&gt;Phone +49 8382 98 520&lt;br&gt;<a href="mailto:info@labortechnik.com">info@labortechnik.com</a></td>
<td>Syngene G:Box Chemi XXB&lt;br&gt;UV light, white/red&lt;br&gt;blue/green/IR&lt;br&gt;incident light, white light transmission, blue light converter, UV transilluminator</td>
<td>9 MP camera, QE greater than 73% @ 425 nm, motor-driven lens (0.95) with auto-focus and automatic zoom, motor-driven 7-position filter wheel with UV filter</td>
<td>Fluorescence, visible, chemiluminescence, IR and 2D applications</td>
<td>On request</td>
<td></td>
</tr>
<tr>
<td><strong>MoBiTec</strong>&lt;br&gt;Goettingen, Germany&lt;br&gt;Contact: Arne Schulz&lt;br&gt;Phone +49 551 70722 0&lt;br&gt;<a href="mailto:info@mobitec.com">info@mobitec.com</a></td>
<td>GelBox: All-in-One Portable Electrophoresis and Imaging System&lt;br&gt;CCD</td>
<td>1,376 x 1,080 pixel</td>
<td>Gel electrophoresis and imaging camera in a closed system</td>
<td>2,769.–</td>
<td></td>
</tr>
</tbody>
</table>
## Gel Documentation Systems

<table>
<thead>
<tr>
<th>Company/Distributor</th>
<th>Name of Product</th>
<th>Light sources</th>
<th>Image resolution</th>
<th>Miscellaneous, Specialities, Generality</th>
<th>Price (EUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FastGene Blue GelPic LED Box</td>
<td>Blue LED transilluminator, white LED light transilluminator</td>
<td>9 MP, CMOS camera</td>
<td>No damage to DNA by UV light</td>
<td>Safe working conditions</td>
</tr>
<tr>
<td></td>
<td>FastGene Blue/Green GelPic LED Box</td>
<td>Blue/green LED transilluminator: Visual light</td>
<td>9 MP, CMOS camera</td>
<td>No damage to DNA by UV light</td>
<td>Safe working conditions</td>
</tr>
<tr>
<td></td>
<td>FastGene FAS-Digi</td>
<td>Blue/green LED transilluminator: Visual light</td>
<td>16 MP LiveMOS camera</td>
<td>No damage to DNA by UV light</td>
<td>Safe working conditions</td>
</tr>
<tr>
<td></td>
<td>FastGene FAS-V</td>
<td>Blue/green LED transilluminator: Visual light</td>
<td>Scientific grade 2 MP CCD sensor camera with in-built computer</td>
<td>No damage to DNA by UV light</td>
<td>Safe working conditions</td>
</tr>
<tr>
<td>ProteinSimple</td>
<td>FluorChem R</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>8.3 MP CCD camera</td>
<td>-30°C, 5 minute cool down</td>
<td>Versatile and powerful multi-mode imager</td>
</tr>
<tr>
<td>a Bio-Techne brand</td>
<td>FluorChem M</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>8.3 MP CCD camera</td>
<td>-30°C, 5 minute cool down</td>
<td>Multi-colour fluorescent Westerns</td>
</tr>
<tr>
<td></td>
<td>FluorChem E</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>8.3 MP CCD camera</td>
<td>-30°C, 5 minute cool down</td>
<td>High-resolution</td>
</tr>
<tr>
<td></td>
<td>FluorChem Q</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>4.2 MP CCD camera</td>
<td>Versatile and flexible fluorescent imaging</td>
<td>On request</td>
</tr>
<tr>
<td></td>
<td>FluorChem HD2</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>4.2 MP CCD camera</td>
<td>Versatile and flexible chemiluminescent imaging</td>
<td>On request</td>
</tr>
<tr>
<td></td>
<td>FluorChem FC3</td>
<td>See above</td>
<td>1.4 MP CCD camera</td>
<td>Economical gel documentation</td>
<td>Upgradeable to chemiluminescence</td>
</tr>
<tr>
<td></td>
<td>Alphalmager HP</td>
<td>Trans UV fluorescence, Trans (white, blue)</td>
<td>1.4 MP CCD camera</td>
<td>Economical gel documentation</td>
<td>On request</td>
</tr>
<tr>
<td>Serva Electrophoresis</td>
<td>Serva Musketeer</td>
<td>White light, RGB and UV transilluminator</td>
<td>6 MP (cooled CCD)</td>
<td>Gel format: up to 260 mm x 200 mm</td>
<td>Absolute sealed darkroom, moveable 3-level platform for chemiluminescence</td>
</tr>
<tr>
<td>Heidelberg, Germany</td>
<td>Serva BlueImager</td>
<td>RGB and white light LED transilluminator</td>
<td>2 MP (CCD camera)</td>
<td>High sensitivity (up to 1 ng protein/band, spot)</td>
<td>Ready for DIGE, multiplex analysis of large format gets up to 255 mm x 195 mm</td>
</tr>
<tr>
<td><a href="http://www.serva.de">www.serva.de</a></td>
<td>Serva Digital Imaging and Analysis System III (DIAS-III)</td>
<td>UV, blue and white light transilluminators</td>
<td>12 MP (SLR camera)</td>
<td>DIAS-III-B: Darkroom (420 x 550 x 520 mm) incl. camera, UV filter and filter holder</td>
<td>DIAS-III: DIAS-III-B incl. GelScan 6.0 1D analysis software</td>
</tr>
<tr>
<td></td>
<td>Serva BlueCube</td>
<td>UV transilluminator (312 nm)</td>
<td>9 MP (CMOS sensor)</td>
<td>BC-300: Including UV filter, magnetic shield for safe cutting of bands, as well as gel capture and 1D analysis software</td>
<td>BC-300L: BC-300 incl. laptop computer</td>
</tr>
<tr>
<td></td>
<td>Serva Blue/White Light Table</td>
<td>Blue and white light LED</td>
<td>--</td>
<td>Viewing area: 180 mm x 120 mm</td>
<td>Adjustable light intensity (3 levels)</td>
</tr>
<tr>
<td></td>
<td>Bio-5000 Plus VIS Gel Scanner</td>
<td>White light LED</td>
<td>Up to 4,800 dpi</td>
<td>Scan area: 216 mm x 254 mm</td>
<td>Autofocus and calibration</td>
</tr>
</tbody>
</table>
### Products

#### Gel Documentation Systems

<table>
<thead>
<tr>
<th>Company/Distributor</th>
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<th>Price [EUR]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serva</strong> (continued)</td>
<td>Bio-1000F Fluorescence Gel Scanner</td>
<td>Blue light LED (460-490 nm)</td>
<td>600 dpi</td>
<td>Detection limit of 0.04 ng DNA/ band with Serva DNA Stain Clear G</td>
<td>3,250.–</td>
</tr>
<tr>
<td><strong>Syngene</strong> Cambridge, UK</td>
<td>G: Box F3</td>
<td>Trans UV</td>
<td>3.8 MP up to 15.3 MP effective resolution</td>
<td>Entry level gel doc system for fluorescence and visible applications</td>
<td>6,500.–</td>
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<tr>
<td><strong>Syngene</strong> Cambridge, UK</td>
<td>InGenius3</td>
<td>Trans UV, white and blue</td>
<td>3 MP</td>
<td>Low budget gel doc and analysis system for fluorescence applications</td>
<td>3,500.–</td>
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<td><strong>Syngene</strong> Cambridge, UK</td>
<td>U:Genius3</td>
<td>Trans UV, white and blue</td>
<td>3 MP</td>
<td>Complete imaging system for fluorescence applications</td>
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<td>NuGenius</td>
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<td>5 MP</td>
<td>Integrated system</td>
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<td>NuGenius+</td>
<td>Trans UV, white and blue</td>
<td>5 MP</td>
<td>Designed for stain-free applications</td>
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<td><strong>GeneGnome XRQ</strong></td>
<td>None</td>
<td>4 MP up to 16 MP effective resolution</td>
<td>Dedicated system for chemiluminescence imaging</td>
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<td></td>
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<tr>
<td><strong>GeneGnome XRQ</strong></td>
<td>G: Box Chemi XRQ</td>
<td>Trans UV, white and blue</td>
<td>4 MP up to 16 MP effective resolution</td>
<td>Next generation CCD camera with higher quantum efficiency and lower noise levels</td>
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<td>G: Box Chemi XX6</td>
<td>Trans UV, white and blue</td>
<td>6 MP up to 18 MP effective resolution</td>
<td>Extended range of applications, covering fluorescence and chemiluminescence</td>
<td>21,500.–</td>
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<tr>
<td><strong>GeneGnome XRQ</strong></td>
<td>G: Box Chemi XX9</td>
<td>Trans UV, white and blue</td>
<td>9 MP up to 27 MP effective resolution</td>
<td>Compact, multi-application imaging system</td>
<td>19,000.–</td>
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<tr>
<td><strong>GeneGnome XRQ</strong></td>
<td>G: Box mini 6</td>
<td>Trans UV, white, blue, red, green, IR</td>
<td>6 MP up to 18 MP effective resolution</td>
<td>High resolution images per one click</td>
<td>6,500.–</td>
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<tr>
<td><strong>GeneGnome XRQ</strong></td>
<td>G: Box mini 9</td>
<td>Trans UV, white, blue, red, green, IR</td>
<td>9 MP up to 27 MP effective resolution</td>
<td>Minimal bench space</td>
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<td><strong>Sysmex</strong> Norderstedt, Germany</td>
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<td>Epson V600 scanner, white and IR LED</td>
<td>Optical: Main 6,400 dpi x sub 9,600 dpi</td>
<td>Electrophoresis systems</td>
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<td>SAS-3 and SAS-4</td>
<td>Epson V800 scanner, white and IR LED</td>
<td>High resolution lens 4,800 x 9,600 dpi</td>
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<td><strong>ThermoFisher Scientific</strong> <a href="http://www.thermoscientific.com">www.thermoscientific.com</a></td>
<td>E-Gel Imager</td>
<td>UV, blue</td>
<td>12-bit, 1.3 MP camera</td>
<td>Compact, affordable, easy-to-use imaging system</td>
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<td><strong>Vilber Lourmat</strong> Eberhardzell, Germany <a href="http://www.vilber.de">www.vilber.de</a></td>
<td>Fusion Edge (New)</td>
<td>More than 20 different Trans and Epi light sources</td>
<td>Scientific grade b/w camera, 16-bit, DMax7 (+67°C) and DMax6 (-55°C) as well as Fusion optics available</td>
<td>Highly flexible imaging platform</td>
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<td><strong>Vilber Lourmat</strong> Eberhardzell, Germany <a href="http://www.vilber.de">www.vilber.de</a></td>
<td>Infinity CX5</td>
<td>Integrated Epi WL-LED</td>
<td>5.0 MP scientific grade b/w camera (made in Germany), 16-bit, max. image resolution: 20 MP</td>
<td>Comfortable handling</td>
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<td><strong>Vilber Lourmat</strong> Eberhardzell, Germany <a href="http://www.vilber.de">www.vilber.de</a></td>
<td>Quantum CX5</td>
<td>Integrated WL-LED and optional UVA/UVB Epi illumination</td>
<td>5.0 MP scientific grade b/w camera (made in Germany), 16-bit, max. image resolution: 20 MP, motorised zoom lens</td>
<td>Comfortable handling</td>
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<td>Bio-Print CX4</td>
<td>Integrated UV or Super-Bright trans illumination light sources</td>
<td>2.0 MP scientific grade b/w camera (made in Germany), 16-bit, max. image resolution: 5.0 MP, motorised zoom lens</td>
<td>Basic system for routine gel documentation</td>
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<td><strong>Vilber Lourmat</strong> Eberhardzell, Germany <a href="http://www.vilber.de">www.vilber.de</a></td>
<td>E-Box CX5 TS</td>
<td>Integrated or changeable: different UV and LED transillumination light sources</td>
<td>5.0 MP scientific grade b/w camera (made in Germany), 16-bit, max. image resolution: 20 MP, motorised zoom lens</td>
<td>Stand-alone system</td>
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<td><strong>Vilber Lourmat</strong> Eberhardzell, Germany <a href="http://www.vilber.de">www.vilber.de</a></td>
<td>Doc-Print VX5</td>
<td>Different UV or LED transillumination</td>
<td>2.0 MP scientific grade b/w camera</td>
<td>Stand-alone system</td>
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**Bench philosophy (70): The second generation of patch clamp recording**

**Patch Clamp 2.0**

41 years after Erwin Neher’s and Bert Sakmann’s seminal _Nature_ paper, describing the first patch clamp recordings of ion channels, new patch clamp techniques open the doors to the functional dissection of synaptic circuits.

Within the first generation of patch clamp, we encounter the classical applications that include the excised patch (inside-out and outside-out) and the whole-cell modes. An excised patch requires the detachment of a small piece of the membrane for its electrophysiological analysis. It is the tool of choice for the analysis of single-channel properties. In whole-cell recordings, the pipette gains access to the intracellular medium and can deliver dyes, small molecules or genes. It is the approach used to study voltage and current fluctuations across the membrane of an entire neuron.

The second generation of patch clamp techniques covered three major applications: subcellular patch clamp techniques, multiple simultaneous patch clamp recordings and in vivo recordings.

Subcellular patch clamp techniques are the minimalistic refinement of classic patch clamp experiments. They have opened the door for the study of new functional compartments, such as axons and dendrites, thanks to technical developments in micro-manipulators, microscopes and brain slicing methods. Micromanipulators of outstanding mechanical stability and minimal pipette drift (in the micrometre range) facilitate stable recordings from small structures. Microscopy methods based on transmitted sources of illumination (infrared and Dodt microscopy) and fluorescence (e.g. confocal and two-photon), allowed users to move from a blind approach to a visually-guided patching experience. Finally, the new generation of brain slicing techniques is better-suited for delicate neuronal structures.

Applications of subcellular techniques are suitable for the analysis of neuronal subcompartments and the study of synaptic transmission. In the first group, we find the excised patch mode, a subcellular variant of the outside-out configuration that allowed the mapping of channel densities along the dendrites. This breakthrough paved the way for later refinements in subcellular patch clamp, involving the direct measurement of dendritic voltage changes with two or more microelectrodes. These experiments changed the view of the dendrite as a merely passive structure and opened a new field focussed on dendritic integration.

Similarly, recordings from axons have demonstrated that the axon’s initial segment (AIS) contains a high density of sodium channels. Hence, the AIS has been implicated in the generation of action potentials and pinpointed as the central processing unit of the neuron. Subcellular patching permits access to small postsynaptic boutons (1 µm diameter) that impinge on sensory hair cells and has shed light on the working mode of sensory ribbon synapses.

**Paradigm change**

When subcellular patching arrived in the field of synaptic transmission in the mid-1990s, the experimental paradigm to study synapses changed from the classic frog neuromuscular junction to mammalian central synapses. The calyx of Held, for example, offers a model with many advantages. It is a giant auditory synapse, with a presynaptic terminal connected to a single postsynaptic cell body. The experimenter can patch both elements simultaneously and introduce drugs into their cytoplasm to test their effects on neurotransmission. Calcium chelators are available to spatially and temporally restrict the spread of calcium ions in the presynapse. It is also possible to homogeneously raise the concentration of calcium using caged compounds, such as DM-nitrophen. This molecule binds to calcium and releases it during a flash of ultraviolet light.

The excitatory synapse between the mossy fibre and the CA3 pyramidal cell in the hippocampus is probably the most representative cortical synapse that has been recently studied with subcellular techniques. Still considered a large synapse; it allows the simultaneous presynaptic patch-clamp recording from a bouton (3-5 µm), while postsynaptically accessing a CA3 pyramidal neuron. The mossy fibre-CA3 pyramidal neuron synapse represents the canonical form of the presynaptic expression of long-term potentiation (LTP).

Dual recordings at this synapse have unveiled an endogenous buffer that controls calcium between its entry point and the vesicle fusion sites (Science 343, 665-70). More importantly, this synapse is, to date, the only known cortical synapse with a one-to-one communication. It permits the discharge of an action potential with a single presynaptic stimulation, several seconds after a high-frequency activity has occurred (conditional detonator). Concerning its detonation properties, the mossy fibre-CA3 synapse is also called the “teacher synapse”.

Subcellular techniques have contributed to the most intriguing findings in neuroscience. For example, against Cajal’s principle of information flow from dendrites to soma, an action potential can travel back from the axon to the dendrites. The generation of action potentials is not an exclusive property
of axons, since dendritic spikes are present in almost all neuronal types. Axonal patch clamp has permitted the molecular identification of ion channels with very fast activation kinetics and optimal energy consumption (Nav1.2, Kv1.1 and Kv3.3). Moreover, owing to this technique, new ways of encoding information have been suggested (analogue versus digital encoding) that may enrich the repertoire of possible synaptic communication between cells.

When the study of synaptic transmission extended its formal biophysical approach to include neuronal networks, it created a new research field. Functional connectomics aims at investigating the neuron’s activity (i.e. function) inside its wiring diagram (i.e. connectome). Patch clamp is well-suited for studying this relationship. Because synapses bridge the information contained in the action potentials fired by a cell (presynaptic side) to a voltage response in the target neuron (postsynaptic side), simultaneous recordings from both neurons (i.e. paired recordings) offer a logical approach to investigate functional connections.

By evoking one presynaptic action potential, we can characterise many features of unitary synaptic responses at the biophysical level (i.e. response size, the number of functional contacts, release probability, etc.). When we elicit a train of action potentials, we can further evaluate the time variation of the response (i.e. short-term dynamics), which is a synaptic signature of a functional connection between two neurons.

Paired recordings could also precisely control the timing of action potentials occurring in two neurons. They provide the ultimate way to address the Hebbian postulate directly, which suggests that synaptic plasticity occurs when pairs of neurons fire in association. For instance, in pairs of layer 5 pyramidal neurons of the rat somatosensory cortex, it is possible to induce plasticity changes: the strength of the connection between neurons can be modified by just varying the timing between the action potentials of pre- and postsynaptic cells (Science 275, 213-15).

Inducing changes in plasticity
In connected pairs of neurons, the natural order of activation (first presynapse, second postsynapse) enhances synaptic responses, whereas the reversal of the sequence (i.e. postsynapse before presynapse) produces the opposite effect. Thus, the rules of spike timing-dependent synaptic plasticity (STDP), the canonical form of synaptic plasticity between excitatory neurons, were discovered with the improvement of patch clamp methods.

An extension of the paired recording technique has been achieved by heroically increasing the number of simultaneous patch clamp pipettes added to a given preparation. By simultaneously patching several neurons in the visual cortex (Science 353, 1117-23), researchers demonstrated functional connectivity principles (motifs), provided for the first time (Plos Biol 3, e68).

Increasing the number of simultaneous paired recordings offers a distinct advantage; in a quadruple simultaneous recording configuration, six paired configurations can be tested, resulting in a total of 12 putative synaptic connections. However, if we use the same number of electrodes (four) in a standard paired-recording configuration, only two paired recordings and four possible synaptic connections are possible. To date, 12 is the largest number of cells recorded by simultaneous patch clamp recording.

Mouse genetic meets patch clamp
A modern twist on this technique is recording from one or several neurons of choice by exploiting genetically labelled neuronal sub-classes in transgenic mice lines. We live in exciting times where the symbiosis between mouse genetics, fluorescence imaging and advanced patch clamp techniques will unravel the functional microcircuits in neuronal networks.

Classically, blind patch clamp recordings have been used to record neurons in brain slice preparations, in the absence of any visual guidance. Just when this method was in decline, it experienced a sudden renaissance in the in vivo recording technique. In the in vivo patch clamp technique, a small brain craniotomy enables blind neuronal access to different parts of the brain following stereotactic coordinates.

This technique has the edge over its extracellular counterparts, such as local field, silicon probes or tetrode recordings. The whole-cell mode permits the unequivocal attribution of firing patterns to identified neurons. It also allows the detection of subthreshold fluctuations (e.g. postsynaptic potentials and currents) and an adequate labelling of patched cells. At present, it comes at the expense of relatively short recording times, limited possibilities for pharmacological intervention and the evaluation of a restricted repertoire of behaviours. Despite these limitations, neuroscientists have devised some ingenious implementations. Whole-cell recordings in fully anaesthetised animals are now in bloom. The low resistance access serves as an ideal intracellular conduit for delivering genes or dyes to neurons in their natural context, making possible detailed reconstructions of neurons. In vivo recordings combined with subcellular patching techniques allowed unprecedented access to the dendrites in the superficial layers of the visual cortex and the axons of the cerebellar mossy fibres. By using patch clamp in vivo, together with local field recordings, we can track the local interactions between a single neuron and the circuits that surround it.

Nowadays, recording in fully awake animals with access to deep brain structures is no longer fiction. It is possible to obtain whole-cell recordings from cortical neurons in awake rodents, while they move on a spherical treadmill or run on a linear belt, using either real sensory cues or virtual environments. Despite being in their infancy, on vivo whole-cell recording techniques have contributed to the discovery of several new principles in neuroscience. We now know that the dendrites of pyramidal neurons from layer 2/3 in the mouse visual cortex are tuned to specific visual features and that dendritic spikes selectively match the preferred stimulus orientation (Nature 503, 115-20). Growing evidence supports that CA1 pyramidal cells in the hippocampus are the cells that fire when an animal enters a particular location (place cells).

Inhibitory hippocampal neurons, in contrast, show little spatial tuning, although there is evidence that parvalbumin-positive interneurons in the neocortex respond to sensory stimulation. Since its origins, this technique has stirred the scientific debate. One of its most intriguing findings is the sparse activity in granule cells, the input layer of the hippocampal formation. These cells can fire bursts of up to 100 spikes per second, leading to the proposal that the granule cell network could provide a way of compressing spatial information. This mechanism can potentially represent one of the most robust encoding strategies of the brain.

With the precise control of gene expression, a careful targeting of neurons and the assessment of an enriched palette of behaviours, we will soon be able to decipher the single-cell correlates of specific brain functions. This combined approach will hopefully reconcile single-cell computations with the general principles of population coding.

Jose Guzman & Peter Jonas
We are a visual species. When we understand something, we say, “I see”. Someone with a clear plan for the future is said to “have vision”. When we finally understand something, we talk about the “light coming on”. We avoid reading books with no pictures and the GUI has displaced the terminal.

One quarter of our brains is dedicated largely to visual processing. Is that the reason, perhaps, why we find visual images so powerful? Journal covers are now stunning pieces of art with glaring colours. Show someone a picture of a brain lighting up under fMRI and they’ll believe anything you say. Although biologists, in their envy of the “hard” sciences, have often tried to emulate the abstraction of mathematics, at the end of the day, biologists still go by the old saying, “seeing is believing”.

Imaging is a way of opening up the invisible world through the medium of sight. Sure, there are machines that spew out lists of abstract numbers that, when expertly interpreted, tell us how close proteins get to one another, how wide a mitochondrion is, or how deeply into a cell the membrane can invaginate. But when we see something with our own eyes, we open things up to our native ability to instantly gain an intuitive understanding of what is going on. Microscopes are a prosthesis to leverage the amazing natural power of our brains.

Now, here is the point I have been angling my way to: there are some big things happening in cell imaging and, if what I have been philosophising about is actually true, that means big things will be soon happening in biology, too. So what are these big things that have been happening in the imaging world? Two major developments stand out: breaking the diffraction limit and combining together diverse imaging approaches into one approach, using a family of methods called “correlative imaging”.

Remember being told at school that you cannot image anything to a resolution greater than half of the wavelength of light? The reason we were given had something to do with diffraction – as you approach a value equal to half the light’s wavelength, diffraction causes single spots to look like fuzzy discs. To understand why, imagine for a moment a feature you are trying to look at, a spot, say, roughly half the wavelength of the incident light. As light passes by either side of the spot, it gets diffracted. This bending of the light means that it gets spread out around the spot. So, what you actually see is not a point at all but instead something like a fuzzy disc – the so-called “Airy disc”.

One big blob

Now, imagine two such spots next to each other. If the Airy disc is bigger than the separation between the spots, you won’t be able to distinguish them apart. They will look like just one big blob. The point to remember is that this is a fundamental consequence of the wave nature of light and no amount of magnification or bigger lenses or any other workaround you can think of can overcome it. This phenomenon sets a theoretical limit of resolution of about 300 nm for any optical microscope.
But like some other things we were told at school (and if someone reading this taught biology at Devonport High School in the 1970s please contact me – I was right about that photosynthesis experiment), this story is not quite true. Indeed, successes in effectively overcoming the diffraction limit is one of the key developments that has made the new field of correlational microscopy so exciting over the past decade.

So, just how have they broken the diffraction barrier? You probably already know one answer to that – electron microscopy. The basic idea here is to replace the beam of photons used in optical microscopy with a beam of electrons. Electrons in a beam have a much shorter wavelength, hence the minimum size at which you start to get diffraction interference is lower. This is how one version of EM, Transmission Electron Microscopy (TEM), works; whereas its sister technique, scanning electron microscopy (SEM), flashes a beam onto the surface of the target material and the effects resulting from this – back-scattered electrons, secondary electrons and X-rays, for example – are interpreted back into an image.

Then there is confocal imaging. Modern confocal imaging uses a laser to ensure that only a very finely defined spot of the sample is illuminated. Because only this spot is illuminated, there is no (or at least very little) light from other sources to degrade the image. This doesn’t, however, get over the diffraction problem because you will still get Airy discs. All the same, whereas the best optical microscopes cannot get better than around 200 nm, confocals get down to about half of this value, partly because of the pinpoint illumination and partly because you can use different wavelengths.

Breaking the diffraction barrier

But that’s cheating, you tell me: neither of those really break the diffraction barrier, they just move it. Okay, point accepted. There are still other ways, in which the diffraction barrier has genuinely been broken and a lot of them are based on looking at individual molecules. They comprise a bag of tricks to make sure that only one molecule is excited at a time, resulting in what has been called “Super-resolution light microscopy” (SLM). Take STED, for example. STED stands for Stimulated Emission Depletion and the idea is to isolate the fluorescence from a single label molecule. How is that done?

A powerful laser is shone onto the region surrounding a single spot. This forces the electrons of the fluorophore into the ground state, keeping them from emitting fluorescence. A small patch in the centre, however, is left untouched and free to emit. The ring of grounded fluorophore molecules is at a distance that corresponds to the diffraction length of the light, so you don’t get destructive interference. STED won its inventor, Stefan Hell, the Nobel Prize in Chemistry in 2014.

Another method is called STORM (STochastic Optical Reconstruction Microscopy). Imagine you have a structure in your cell that has been labelled with a fluorescent probe. You stimulate the probe at just the right level, so that only a small fraction of the molecules gets excited. In the brief time it takes for them to emit and drop back into their dark state, you measure the location of the emitted signal. If you get the level of illumination quite right, you are statistically unlikely to have all that many molecules close enough to each other to create any destructive interference. With a bit of mathematical post-processing, you can re-assemble a detailed picture of the target. These are just two examples of what is turning out to be something of an explosion of super-resolution imaging methods, which are now bringing the resolution down to the 10 nm range and even below. Impressive but still not quite as good as electron microscopy, which easily gets down to 1 nm. There is, however, an important point here that can easily be missed. Super-resolution imaging does not get down to EM resolutions but it is getting close enough, to make it worthwhile to find ways of combining EM and SLM.

Synergistic effects

Why is that so important? Because combining two methods amplifies their respective good points and erodes their bad points. In fact, our brains are doing this all the time. When you listen to someone speaking, you are combining auditory information (their speech) with visual information (the movements of their lips). When information from one modality is not so good (the person talking to you is also eating a doughnut), the other channel makes up for it. The whole becomes greater than the sum of the parts.

Now, let’s apply this to imaging. What are SLM’s good points compared to EM? For one, there are lots of fluorescent probes and they are easy to make, whereas with EM you have to come up with something electron-dense. Also, with SLM you can image without damaging the cell, whereas to do EM you need to freeze the cell (to preserve water content), fix it and put it under a high vacuum. EM has its own advantages, too – resolution being the main one. There are so many benefits in combining SLM and EM that they have given it a name: CLEM (Correlative Light Electron Microscopy). The idea behind CLEM is to do SLM and EM on the same preparation.

Imagine, for example, the distribution of a fluorescently-labelled protein at the 50 nm scale on wet, perhaps even live, cells. But you want to know where the protein is located at the nanometre scale, so that once you have finished running SLM, you then go and put the sample into an electron microscope to get a high-resolution image of the same material. You would then correlate the two sets of images, to draw inferences that span the two different scales. In one sense, we have been doing that all the time without realising it – think of those figures where one has the whole cell in view and an inset has a magnified region. CLEM, and indeed, all correlational microscopy techniques, are more thorough ways of doing just that.

But there are many problems with trying to do two different techniques on the same tissue. First of all, the two tech-
niques treat the tissue in very different ways because they have very different requirements. EM, for example, needs the tissue to be strongly fixed and the strong fixatives used can quench the fluorescence of the probe. Again, SLM has to be done using wide-aperture, oil-immersion objectives and that means you need to mount the preparation under a glass coverslip. But you can’t use glass in EM because the glass is non-conductive and that means you get charge build-up, which ruins the image. In short, the preparation requirements for EM and SLM are at many points completely incompatible and mutually exclusive. One way of overcoming this is to do them in series, one after the other. Do your SLM on a wet, possibly living, cell first, then go and do the EM. But even this brings quite a few problems. Think about that manipulation step – after the SLM step you then have to transfer the preparation from its glass coverslip onto an EM grid. Are you sure you won’t bend, stretch or otherwise distort the preparation in the process? And what about distortions caused by the dehydration, fixing and embedding that is needed for EM? Remember the scale we are talking about here: even just a few nanometres of movement will make correlation very difficult, to say the least.

Preventing distortions

Several labs have come up with ingenious ways of getting around this. Wojcik et al. came up with the solution of coating cells with a layer of graphene (Nature Communications, 6:7384). Graphene is all but invisible to the light used in SLM but is electroconductive, so it can be used in EM. Other labs have solved the problem by thinking carefully and strategically about exactly which methods they are going to combine. For example, several labs have used cryofixation, in which cells are plunged into a cryogen (e.g. liquid helium), vitrifying the cell contents without allowing the water to crystallise. Ultrastructure is preserved, obviating the need for fixation. In this way, SLM and EM can be done on the same sample under the same, or similar, preparation conditions. However, it does mean doing all the experiments at below -140 °C and it is hard to predict how a fluorophore is going to act at those temperatures. Besides, microscope objectives will need a lot of additional features engineered into them, if they are to work under these conditions.

An entirely different set of problems arises because data from two different scales are being combined. The task of image registration is the process of identifying corresponding positions in the two imaging results. It is a bit like looking at two maps: one covers the whole county, the other just your local village. To get the benefit of correlating the two maps, you have to match up landmarks in both of them. This can get quite difficult. The two maps may use different colour codes (motorways are blue in one, white in the other, for example) and different sets of symbols (one map may not have built-up areas marked) as well as the different scale. The very same problem is faced in the crucial step of finding where, in your 10 nm “map” of a cell, that intriguing blob in the 0.1 nm image corresponds. One way researchers overcome this is to introduce their own fiducial (trustworthy) landmarks. For this approach to work, you have to find a stain that will be visible in both “maps”, for example, both fluorescent and electron-dense – no easy task. The problem of registration is exaggerated when you use serial methods, such as SLM followed by EM, because you never know what distortions you may have introduced, while moving the specimen from the glass slide to the EM grid. Remember, we are working here in the 0.1 to 10 nm range of scales, so there is not much tolerance allowed.

Image analogies

Here again, researchers have demonstrated ingenuity in getting around this problem. Tian Cao at the University of North Carolina at Chapel Hill and colleagues turned to computer vision to solve the registration problem. In computer vision there is a trick called “image analogies”, in which you give the computer pairs of images and it learns the relationship between them. Cao showed how you could apply the same method to pairs of images, acquired using different imaging technologies (Med Image Anal 18(6):914-26).

Researchers have also been challenged with other aspects of matching two different approaches working at two different scales. Not only do movement or distortion artefacts have to be controlled for, but differences arising from using diverse mechanisms of staining also need to be accounted for. For example, think of imaging a fluorescent probe with SLM and matching it to an electron-dense probe in EM. With any approach, using binding of a probe to a target, there is inevitably a distance between the emitting/absorbing site of the ligand and the actual target, and for many probes that may be quite big. If this distance is significant, relative to the distribution of the target, each of the two techniques introduce an uncorrelated error.

All the same, the potential advantages of correlating microscopy at different scales are compelling enough for many labs to undergo the hard work of overcoming these many challenges. The result is that just about every combination of microscopic technique has been tried in one way or another. And it is not just combining SLM with EM. SLM has also been combined with Atomic Force Microscopy (AFM), in which a vibrating cantilever brushes over a cell surface and works out, at submolecular dimensions, the shape of the landscape it crosses. Recent advances have allowed this to be done at high speed, fast enough in fact...
to observe the dynamics of molecular motors. The big plus from combining AFM with SLM is that the two techniques are much more compatible than, say, SLM and EM.

Correlative approaches aren’t just about combining information over different spatial scales but also over different temporal scales. SLM is still quite slow, thanks to the unavoidable trade-off between resolution and speed. In other words, you get good quality spatial data but poorly resolved (or no) temporal data. So, what happens if you are interested, not only in where things are but also how they are moving or changing over time? One way around this is to correlate SLM with something that works faster, thus combining the spatial data of SLM with temporal data of the complementary technique. An exciting example of this combines SLM with mass spectrometry. Silvio Rizzoli and Johannes Wessels of University of Göttingen Medical Centre combined secondary ion mass spectrometry (SIMS) with STED, to measure protein turnover in specific organelles.

Combining SIMS and STED

SIMS works by applying a beam of particles (such as caesium ions) onto a sample and doing mass spectrometry on the material that is emitted as a result. By scanning across a sample, you can get an image of the isotopic composition of the sample. But the method is low resolution and the data cannot be attributed to organelles. In Rizzoli’s and Wessel’s approach, SIMS was correlatively combined with STED to couple the spatial resolution of the latter with the chemical information of SIMS (Nature Communications 5: 3664).

Some biological questions can only be answered by simultaneously addressing different scales of organisation and this is just the kind of problem at which correlational methods excel. The brain is a case in point. To understand how the brain controls behaviour, we need answers to questions at the molecular, cellular, circuit and whole-brain scales. Several labs have correlatively combined fMRI with optical probes or calcium imaging with scanning electron microscopy. In some cases, even just the very size of some biological macromolecules forces a multi-scale approach. Chromatin, for example, is a grand total of some two metres long (in humans), so a complete understanding of how it is packed into a nucleus requires us to look at it on an astounding-ly wide range of scales. Sure, you can use EM to look at its structure but getting a wider picture is like trying to finding your front lawn on Google Earth – without zooming out. Clodagh C. O’Shea solved this problem by taking a correlational approach that combined electron microscopy tomography (taking optical slices of a sample at different angles, from which a 3D picture can be reconstructed) with a probe (ChromEM) that labels DNA (Science, 357, 6349).

Huge scale difference

This method (ChromEMT) was used to yield new insights into its packing design. But perhaps the prize for the biggest difference in scale goes to a group around Marcel Schaaf and Herman Spink of the Institute of Biology, Leiden University (see figures above), who combined EM with whole-animal imaging, to gain new insights into the way, in which autophagy protects against infection (Autophagy 10:10, 1844-57).

The number of potential applications of correlative imaging is quite literally exponential, because it entails combinatorial strategies. But there are major technical challenges and each of these is likely to be very application-specific. Solutions found in one particular context are unlikely to transfer in detail to another. All the same, now that the power of correlation is making itself clearer, we are likely to see more efforts to solve these challenges. Correlational imaging will, dare I say, really put us in the picture.

Steven Buckingham
New Products

Assay analysis

**Product:** Microplate reader  
**Name & Manufacturer:** 800 TS from Biotek  
**Technology:** The absorbance reader features a colour touchscreen interface with easily programmed onboard software, 6- to 384-well microplate reading, and temperature control and shaking to expand its applications to kinetic assays.  
**Advantages:** The reader is compatible with BioTek’s Gen5 Software, to expand its data collection and analysis capabilities.  
**More Information:** www.biotek.com  
**Phone:** 908 818 9463

Flow cytometry

**Product:** Flow cytometer  
**Name & Manufacturer:** CytoFLEX LX from Beckman Coulter Life Sciences  
**Technology:** The Blue-Red-Violet-Yellow Green-Ultraviolet-Infrared series of the instrument incorporates excitation sources from ultraviolet 355 nm to infrared 808 nm alongside the existing Avalanche photodiode detectors.  
**Advantages:** The cytometer offers excitation sources across the visible spectrum in a standard configuration, opening up possibilities, especially in cancer research.  
**More Information:** info.beckmancoulter.com/CytoFLEX-LX-UV  
**Phone:** +49 2151 3335

Cold storage

**Product:** Undercounter refrigerators  
**Name & Manufacturer:** TSX505 Series from Thermo Fisher Scientific  
**Technology:** The refrigerators are powered by compressor-free V-Drive technology, featuring synchronized temperature management (STeM). Internal conditions are actively monitored and maintained at the desired temperature. V-Drive and STeM provide uninterrupted temperature stability and uniformity throughout the internal chamber. Furthermore, the refrigerators consume up to 37 percent less energy than other models, translating to an average annual cost reduction of up to 30 percent. The undercounter refrigerators use environmentally-friendly refrigerants. Data logging capabilities are easily enabled through a USB port, allowing users to monitor storage conditions in a timely and efficient manner.  
**Advantages:** The compressor-less technology of the refrigerators overcomes the common challenge of ‘humming’ experienced with many lab-grade refrigerators through its whisper-quiet operation at just 35 dBA. This means that the unit can be kept in work areas without disturbing personnel or nearby patients. In addition, with no internal protrusions, such as overhead fans, users can benefit from up to double the storage space compared to similar models.  
**More Information:** thermofisher.com/aacc2017

Transfection

**Product:** Transfection reagent  
**Name & Manufacturer:** Fuse-It-siRNA from Ibidi  
**Technology:** The liposomal carrier, which includes the siRNA, fuses with the cell membrane and then releases the siRNA directly into the cytoplasm. Thus, the siRNA is immediately incorporated into the RISC complex, leading to efficient gene knockdown.  
**Advantages:** The transfection reagent enables rapid and efficient gene silencing, even in sensitive and difficult-to-transfect cells, such as primary keratinocytes.  
**More Information:** www.ibidi.de  
**Phone:** +49 89520461759

Automation

**Product:** Conductive robotic tips  
**Name & Manufacturer:** BlackKnights from Ritter Medical  
**Technology:** The conductivity enables the system to recognise the fluid level and immerse into the liquid only as far as necessary in order to ensure safe pipetting and dispensing. The tips are produced to the highest quality standards under cleanroom conditions and are tested by independent laboratories to be free of DNase, RNase, ATP and pyrogens.  
**Advantages:** To provide more flexibility, 50 μl, 200 μl and 1000 μl conductive tips are also offered for SBS containers. These plastic boxes correspond to the dimensions of a microtiter-/deep-well plate and can thereby be placed at any positions of the worktable.  
**More Information:** www.ritter-medical.de  
**Phone:** +49 8232500345
Ultra low temperature upright freezers

**Name & Manufacturer:**
Twin Guard from Panasonic

**Technology:**
The new models provide an internal capacity of 528 litres and 729 litres, respectively. The freezer cabinet design with chamfered edges and VIP PLUS insulation helps to achieve optimum temperature uniformity within a reduced footprint. The bevel of the outer door sides reduces the space required to the side of the freezer for door opening. The freezers also feature a flexible shelf layout with multiple shelf configurations. Existing inventory racks can be transferred into the new freezers. A colour LCD touch panel allows full user control, even with gloved hands, while the USB port makes transferring logged data to a PC convenient.

**Advantages:**
- Two independent refrigeration systems provide a reliable and stable -86°C ultra low temperature environment. If one system fails, the other can maintain the freezer in the -70°C range until service can be arranged.

**More Information:**
- eu.biomedical.panasonic-healthcare.com/twinguard
- Phone: +31 76 543 3833

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**Benchtop flow cytometer**

**Name & Manufacturer:**
MACSQuant X from Miltenyi Biotec

**Technology:**
With three lasers (405, 488, 638 nm), 10-parameter experiments can be performed in 15 minutes for a 96-well plate and in less than 60 minutes for a 384-well plate. Data from each sample are saved in an individual file, allowing you to either analyse every sample on the fly or access ready-to-analyse data immediately after the plate processing has finished. The instrument enables consistent results with as little as 5 μL uptake volume per sample; it still delivers consistently low coefficient of variation (CV) values, regardless of the chosen flow rate and input volume. The integrated vibration needle can mix every single well of a plate individually. The Orbital Shaker enables 2-dimensional mixing of all samples within the plate at once. This shaker allows for an easy experimental setup and enables users to switch directly between a single tube, tube rack or different plate types.

**Advantages:**
- Thanks to the optimised, compact design, the device fits on a common laboratory work surface and can be integrated either as a stand-alone instrument or as a module in a fully automated cell processing system. The cytometer offers flexibility and versatility in applications in screening facilities as well as in routine laboratories.

**More Information:**
- www.miltenyi-biotec.com/mqx
- Phone: +49 2204 830 620

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**DNA/RNA extraction kit**

**Name & Manufacturer:**
Arcis Prep from Cole-Parmer

**Technology:**
The kit requires two steps that are completed in three minutes, to provide high-quality, PCR-ready templates.

**Advantages:**
- The kit is ideal for applications such as PCR, qPCR, isothermal amplification (LAMP), sequencing, genetic profiling (electrophoresis) and forensic studies. It can also be integrated into automated sample processing or liquid handling systems.

**More Information:**
- ColeParmer.com
- Phone: 1 847 549 7600
Book review on our microbe relatives

Constructing the Tree of Life

Human beings have always been fascinated by their origins. In recent decades, modern biology has disentangled the relationship between all organisms, revealing our kinship with microbes and tracing life back to its roots.

Since Darwin, many attempts have been made to trace the path of evolution and to disentangle kinship among all living beings. For a long time, such studies were solely based on morphological parameters, which, for unicellular organisms, were limited to size and shape. This confinement made taxonomy almost entirely impossible in the bacterial world, with its cells all looking largely the same under a light microscope. Even after the development of electron microscopy, which enabled fascinating insights into the cells of “higher” multicellular organisms, today known as eukaryotes, bacterial cells – due to their density – remained elusive. Consequently, the strikingly different cellular organisation of prokaryotes in comparison to eukaryotes remained concealed.

A scientific bombshell explodes

The seminal discovery of a second group of prokaryotes, indistinguishable from bacteria by morphology but differing vastly in their genetic organisation and other molecular traits, was thus completely unexpected and shook the scientific society. It was only after the dawn of a molecular era, which made single biomolecules susceptible to analysis, that Carl Woese was able to reveal the archaea as a third domain of life, next to bacteria and eukaryota. A prerequisite for his work was Linus Pauling’s description of “semantides”, biomolecules that conserve information about their evolutionary relationship within their sequence, such as DNA, RNA and proteins. As a second step, Woese had to develop methods to track differences in the sequences that he wanted to compare. At first, he used partial digestion, yielding a species-specific digestion pattern, and later turned to determining RNA and DNA sequences directly using Fred Sanger’s dideoxy (or chain termination) method. Today, comparing the sequence of ribosomal RNA genes is the most widely used method for kinship analyses.

Parts of the scientific community were, nevertheless, reluctant to accept the consequence of Woese’s finding that bacteria and archaea, although prokaryotes in their cellular organisation, are evolutionarily as distinct from each other as they are from all eukaryotic organisms, including ourselves. Even nowadays, the debate continues and some researchers propose the expulsion of the term ‘prokaryote’ from the scientific language, because, in their opinion, it blurs the substantial differences between bacteria and archaea.

Who’s who in microbiology

In Kin, John Ingraham, Professor Emeritus at the University of California in Davis and former President of the American Society of Microbiology, describes the milestones on the way to Woese’s pioneering discovery. The book consists of two main and a shorter third part. In the first section, Ingraham retraces the discovery of the Tree of Life. The second section elaborates on common problems in determining evolutionary relationships between organisms that make frequent use of horizontal gene transfer to acquire new traits, like prokaryotes do. Despite this fact, a bacterial species’ core genome remains fairly constant and thus can be used for relationship studies, as Ingraham argues. The third concluding part presents a short outlook – or rather retrospective – on how life might have emerged.

Concurrently, the author provides sort of a Who’s Who of molecular and microbiology by portraying the scientific protagonists, not only with their skills and talents but also with their shortcomings. The reader learns that Woese had a notorious need for recognition and suffered from a subjective rejection of earlier results by his peers. Probably due to this fact, he launched a press conference prior to publication of the archaea’s discovery – a fatal decision, which prompted sensational media coverage and seems to have been more harmful than helpful to Woese’s scientific reputation. Ingraham speculates that this press conference and its consequences might have been one reason, why Woese was never awarded with a Nobel Prize, despite his undisputed achievements.

Inside stories and more

Notably, it is the many side stories about well-known, lesser-known and underestimated researchers, their conflicts and personal tragedies as well as the role of coincidences in science that make the book diverting and worth reading. For instance, Ingraham explains why Francis Crick and James Watson solved the structure of the DNA double helix instead of Linus Pauling, who seemed to be more likely to achieve this goal. But for political reasons, the double Nobel Prize winner was not allowed to leave the United States and was, therefore, unable to travel to England to discuss results with Rosalind Franklin.

Furthermore, the reader learns that Joshua Lederberg’s Nobel Prize hung from the slim thread of his co-researcher Edward Tatum, who provided the former with E. coli K12, a strain that, in contrast to the more commonly used strain E. coli B, was capable of transduction – and some more intriguing anecdotes on famous life scientists and their startling discoveries.

On the whole, Kin is overflowing with information and provides even molecular biologists, who are familiar with the scientific facts, with enough inside stories to entertain.

Larissa Tetsch

The Washington University School of Medicine, St. Louis (USA) is offering a Postdoctoral Position in Kidney Injury and Repair Mechanisms. The Herrlich Lab (http://www.herrlichlab.org) studies the regulation and biology of metalloprotease-released growth factors, cytokines and their receptors (ectodomain shedding predominantly by ADAM10 and ADAM17) in kidney disease and cancer. Ectodomain cleavage regulates many important signaling steps in inflammation and repair of injured organs, as well as numerous cell fate decisions, e.g. by activation of TNFalpha, Notch or of EGFR signaling pathways.

We use:
- experimental models of acute and chronic kidney disease and cancer in vitro and in vivo in mice
- cutting-edge transgenic mouse technology (Cre-mice; CRISPR-Cas9)
- computational approaches
- translational approaches

The ideal candidate will have a strong background in molecular/cellular biology and biochemistry and experience with the handling of mice. The position will be immediately available and is fully funded for up to three years. To apply please submit a letter describing your interests, CV and contact info for three references to Andreas Herrlich, MD PhD: aherrlich@gmail.com.

Contact: Campus Box 8126, to Andreas Herrlich, MD PhD - Associate Professor of Medicine, 660 S. Euclid Ave, 63110 St. Louis, MO (USA)
Calendar

2017


10/9–10/11 Barcelona (ES) Defence is the Best Attack: Immuno-Oncology Breakthroughs (EACR Conference), Info: www.eacr.org/conference/immuno-oncology


10/12–10/15 Estoril (PT) 19th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy, Info: www.esb.org

10/15–10/17 Cologne (DE) 33rd Ernst Klenk Symposium in Molecular Medicine – “Tissue Regeneration, Wound Healing and Fibrosis: Translating Basic Concepts into Regenerative Therapy”, Info: www.cmcc.uni-koeln.de/de/events

10/16–10/17 Ghent (BE) 2nd Conference on Next-Generation Antibodies and Protein Analysis, Info: http://vibconferences.be

10/17 Munich (DE) Epigenetics Spotlight Meeting, Info: www.abcam.com/events


10/19–10/20 Riga (LV) 2nd International Conference in Pharmacology, Info: www.icp2017riga.lu.lv

10/23–10/24 Berlin (DE) 8th World Congress on Targeting Mitochondria, Info: www.targeting-mitochondria.com

10/23–10/25 Vienna (AT) 7th Symposium on Structural Proteomics, Info: www.structuralproteomics.net


10/26–10/27 Berlin (DE) 5th World Congress on Targeting Microbiota, Info: www.microbiota-site.com

10/29–11/1 Berlin (DE) Protecting the Code: Epigenetic Impacts on Genome Stability – Conference of the European Association for Cancer Research (EACR), Info: www.eacr.org


11/2–11/3 Cambridge (UK) Big Data World Congress 2017 – Harnessing the Power of Big Data in Precision Medicine, Info: www.terrapinn.com/conference/biodata

11/2–11/4 Heidelberg (DE) EMBL Conference on Quantitative Principles Biology, Info: www.embl.de/training/events

11/5–11/8 Heidelberg (DE) EMBO Conference on Cancer Genomics, Info: www.embl.de/training


11/6–11/7 London (UK) 6th Annual Cell Culture and Bioprocessing Congress, Info: www.cellculture-congress.com


11/8–11/10 Weimar (DE) 21st Joint Meeting on Signal Transduction: Receptors, Mediators and Genes, Info: www.sigtrans.de/meeting.html

11/9-11/10 London (UK)

11/10 London (UK)
London Chromatin Meeting, Info: www.abcam.com/events

11/10 Nottingham (UK)
Hydrogen Bonds & DNA, Info: www.biochemistry.org/Events

11/12-11/14 London (UK)
Signal Transduction in Health and Disease – The Francis Crick Institute and Dundee University Life Sciences Joint Symposium, Info: http://bit.ly/2gg0a3u

11/12-11/14 Heidelberg (DE)

11/13-11/14 Paris (FR)
9th International Conference on Bioinformatics, Info: http://bioinformatics.conferenceseries.com

11/13-11/15 Paris (FR)
9th International Conference on Proteomics, Info: www.proteomicsconference.com

11/13-11/17 Lisbon (PT)
9th Annual PEGS Europe – Protein and Antibody Engineering Summit, Info: www.pegsummit europe.com

11/14-11/15 Luxembourg (LU)
12th International Conference on Data Integration in the Life Sciences (DILS 2017), Info: www.elisa-project.lu/en/dils-2017

11/14-11/17 Cambridge (UK)
Wellcome Trust Conference on Epigenomics of Common Diseases, Info: https://coursesandconferences.wellcomegenom campus.org/ Conferences.wt

11/15-11/17 Lisbon (PT)
2nd Annual World Preclinical Congress Europe, Info: www.worldpreclinical europe.com

11/16-11/17 Berlin (DE)

11/16-11/17 Heidelberg (DE)
EMBL Conference on Revolutions on Structural Biology: Celebrating the 100th Anniversary of Sir John Kendrew, Info: www.embl.de/training/ events/2017/JKS17-01

11/20-11/22 Cambridge (UK)
Wellcome Trust Conference on Human Evolution: Fossils, Ancient and Modern Genomes, Info: https://coursesandconferences. wellcomegenom campus.org/ Conferences.wt

11/27-11/28 Manchester (UK)
Synthetic Biology UK 2017, Info: www.biochemistry.org/Events

11/28-11/29 Brussels (BE)
World Anti-Microbial Resistance Congress / Microbiome World Congress, Info: www.terrapinn.com/conference

11/29-11/30 Madrid (ES)
2nd International Conference on Food Microbiology, Info: https://foodmicrobiology.conferenceseries.com

11/30-12/1 London (UK)
Understanding Translational Research, Info: www.biochemistry.org/Events

12/5-12/7 Heidelberg (DE)
EMBL Conference on Lifelong Learning in the Biomedical Sciences, Info: www.embl.de/training/events/2017

12/6-12/7 Amsterdam (NL)

12/6-12/8 Cambridge (UK)
Wellcome Trust Conference on Target Validation using Genomics and Informatics, Info: https://coursesandconferences. wellcomegenom campus.org/ Conferences.wt

12/7-12/8 Basel (CH)
Helminth Infection: From Transmission to Control – Swiss TPH Winter Symposium, Info: www.swisstph.ch/en

12/7-12/8 Strasbourg (FR)
Meeting on Glia and Microglia, Info: www.neurex.org/events

12/11-12/13 Cambridge (UK)
New Approaches for Investigating Nascent Peptide Folding, Info: www.biochemistry.org/Events

12/11-12/13 Edinburgh (UK)
Protein Power: From Proteome to Phenotype – Role of Post-Translational Modifications, Info: www.sebiology.org/events

2018

1/8-1/10 Nottingham (UK)
Biochemical Basis of Respiratory Disease, Info: www.biochemistry.org/Events

1/22-1/23 London (UK)
7th Annual Pharmaceutical Microbiology Conference, Info: www.smi-online.co.uk/pharmaceuticals/uk/pharmaceutical-microbiology

1/31-2/2 Cambridge (UK)
Wellcome Trust Conference on Healthy Ageing: From Molecules to Organisms, Info: https://coursesandconferences. wellcomegenom campus.org/ Conferences.wt

2/3-2/9 Lucca/Barga (IT)

2/6-2/7 Cambridge (UK)
Flow Chemistry Europe 2018, Info: www.selectbiosciences.com/ FCE2018

2/10-2/16 Lucca/Barga (IT)

2/12-2/13 Lausanne (CH)
Metabolism and Signaling in the Life Sciences – LS2 Annual Meeting 2018, Info: https://annual-meeting.ls2.ch

2/17-2/23 Lucca/Barga (IT)

2/24-3/2 Lucca/Barga (IT)

2/28-3/2 Cambridge (UK)
Wellcome Trust Conference on Proteomics in Cell Biology and Disease Mechanisms, Info: https://coursesandconferences. wellcomegenom campus.org/ Conferences.wt

3/3-3/9 Lucca/Barga (IT)

3/6-3/7 London (UK)

3/6-3/8 Cambridge (UK)
Wellcome Trust Conference on Single Cell Biology, Info: https://coursesandconferences. wellcomegenom campus.org/ Conferences.wt

3/9-3/11 Mandelieu (FR)
4th International Conference on Hematologic Malignancies at Older Age: Biology and Therapy, Info: www.esh.org

3/10-3/16 Lucca/Barga (IT)

3/11-3/14 Heidelberg (DE)
3/11–3/14 St. Tropez (FR)  
Bacterial Electron Transfer Processes and their Regulation, Info: www.efb-central.org

3/12–3/13 London (UK)  

3/12–3/14 Cambridge (UK)  
Wellcome Trust Conference on Human Reproduction and Development, Info: https://courcesandconferences.wellcomegenomecampus.org/Conferences.wt

3/12–3/18 Amsterdam (NL)  
10th World Mycotoxin Forum, Info: https://worldmycotoxinforum.org

3/15–3/16 Barcelona (ES)  
Clustered Science Technologies For Emerging & Advancements in Structural Biology – International Conference on Structural Biology, Info: http://structubiology.euroscicon.com

3/22–3/24 London (UK)  

3/24–3/28 Dublin (IE)  
Conference on Resolution of Inflammation in Health and Disease, Info: www.keystoneSYMposia.org/1806

3/24–3/30 Lucca/Barga (IT)  


3/26–3/28 Cambridge (UK)  
Wellcome Trust Conference on Genomics of Rare Disease, Info: https://courcesandconferences.wellcomegenomecampus.org/Conferences.wt

3/10–4/13 Munich (DE)  

3/10–4/14 Oxford (UK)  
Therapeutic Targeting of Hypoxia-Sensitive Pathways, Info: www.keystoneSYMposia.org/1801

3/11–3/13 London (UK)  

3/19–3/21 Manchester (UK)  
The Dynamic Cell III, Info: www.biochemistry.org

3/19–3/22 Seville (ES)  
5th Meeting of Regulating with RNA in Bacteria and Archaea, Info: www.ma-meeting.com

3/22–3/23 London (UK)  

3/23–3/28 Dublin (IE)  
Conference on Resolution of Inflammation in Health and Disease, Info: www.keystoneSYMposia.org/1806

3/24–3/30 Lucca/Barga (IT)  


3/10–4/13 Munich (DE)  

3/10–4/14 Oxford (UK)  
Therapeutic Targeting of Hypoxia-Sensitive Pathways, Info: www.keystoneSYMposia.org/1801

3/11–3/13 London (UK)  

3/10–4/13 Munich (DE)  

3/11–3/13 London (UK)  

3/11–3/13 London (UK)  

4/18–4/20 Paris (FR)  

4/19–4/20 Heidelberg (DE)  
EMBL Conference: European Conference of Life Science Funders and Foundations, Info: www.embl.de/training/events/2018

4/19–4/20 London (UK)  
30th Annual UK RNA Polymerase Focused Meeting, Info: www.biochemistry.org/Events

4/23–4/25 Kinsale (IE)  
Microbial Stress: From Systems to Molecules and Back, Info: www.efb-central.org

4/24–4/25 Cambridge (UK)  
Wellcome Trust Conference on Genomics of Brain Disorders, Info: https://courcesandconferences.wellcomegenomecampus.org/Conferences.wt

4/25–4/27 Heidelberg (DE)  
EMBL Conference: The Epitranscriptome, Info: www.embl.de/training/events/2018

5/2–5/4 Dresden (DE)  
Adult Neurogenesis Meeting 2018, Info: www.abcam.com/events/adult-neurogenesis-2018

5/7–5/10 Heidelberg (DE)  
EMBO | EMBL Symposium: DNA Replication – From Basic Biology to Disease, Info: www.embo-emblysymposium.org/symposia/2018

5/9–5/11 Cambridge (UK)  
Wellcome Trust Conference on Mitochondrial Medicine, Info: https://courcesandconferences.wellcomegenomecampus.org/Conferences.wt

5/10–5/12 Frankfurt/M. (DE)  
22nd World Congress on Clinical and Vaccine Immunology: Systems Immunology for Improved Vaccines, Info: http://immunology.euroscicon.com

5/14–5/17 Heidelberg (DE)  
EMBO | EMBL Symposium: Cellular Mechanisms Driven by Liquid Phase Separation, Info: www.embl.de/training/events/2018

5/16–5/20 Lisbon (PT)  
11th International Congress on Autoimmunity, Info: http://autoimmunity.kenes.com/2018

5/19–5/25 Lucca/Barga (IT)  

5/21–5/23 Vienna (AT)  
16th International Pharmaceutical Microbiology and Biotechnology Conference, Info: https://pharmaceuticalmicrobiology.conferenceseries.com

5/23–5/25 Cambridge (UK)  
Wellcome Trust Conference on Curating the Clinical Genome, Info: https://courcesandconferences.wellcomegenomecampus.org/Conferences.wt

5/23–5/25 Heidelberg (DE)  
EMBL Conference: BioMalPar XIV – Biology and Pathology of the Malaria Parasite, Info: www.embl.de/training/events/2018

5/24–5/25 Cambridge (UK)  
Stem Cells and Antibodies in Drug Discovery Europe 2018, Info: http://selectbiosciences.com

5/26–6/1 Leu Diabeters (CH)  
5/26-6/1 Lucca/Barga (IT)  

5/27-5/30 Heidelberg (DE)  
EMBO | EMBL Symposium: Microtubules – From Atoms to Complex Systems, Info: www.embo-embly-symposia.org/symposia/2018

5/30-6/1 Cambridge (UK)  
Wellcome Trust Conference on Longitudinal Studies, Info: https://courseseandconferences.wellcomegenomencampus.org/Conferences.wt

6/2-6/8 Les Diablerets (CH)  

6/2-6/8 Lucca/Barga (IT)  

6/3-5/ Heidelberg (DE)  

6/3-6/6 Gatensleben (DE)  

6/3-6/6 Warwickshire (UK)  
83rd Harden Conference: Autophagy – From Molecules to Disease II, Info: www.biochemistry.org

6/4-6/8 Hannover (DE)  
One Million Genomes: From Discovery to Health, Info: www.keystonegenomysia.org/1861

6/5-6/6 Rotterdam (NL)  
Lab-on-a-Chip and Microfluidics & Organ-on-a-Chip, Tissue-on-a-Chip Europe, Info: http://selectbiosciences.com

6/10-6/13 Madrid (ES)  
41st European Congress of Cyto-logy, Info: www.cytology2018.com

6/10-6/16 Ascona (CH)  
Conference on Bacterial Persistence and Antimicrobial Therapy, Info: www.biozentrum.unibas.ch/bpam2018

6/10-6/14 Aachen (DE)  
15th International Symposium on Dentritic Cells, Info: www.dc-2018.com

6/11-6/13 Cambridge (UK)  
Wellcome Trust Conference on Genomic Epidemiology of Malaria, Info: https://courseseandconferences.wellcomegenomencampus.org/Conferences.wt

6/11-6/14 Berlin (DE)  
19th International Conference on Bacilli & Gram-Positive Bacteria, Info: www.bacillus-2017.de

6/16-6/22 Les Diablerets (CH)  

6/16-6/22 Lucca/Barga (IT)  

6/23-6/29 Cambridge (UK)  
Conference on Cancer and Metabolism, Info: www.abcam.com/events

More events at www.labtimes.org/labtimes/calendar
Lab Tales

Virtual Disaster

Hey, isn't the boss on a conference this week?!

Yes, he said so on Friday.

Something about microbial resistance.

Let's seize the moment and party!

What the...

Oh, it must have been an online conference.

Text: K. Granjaček

Drawings: D. Kapper
Deciphering Cancer

Antibodies to evaluate how cell death and survival impacts tumor development and progression

Download pathways at www.cellsignal.com/cancerpathways