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NETWORKING FOR A CURE

Social Distancing Shatters Alzheimer's Research

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"Do what you can, with what you have, where you are." Theodore Roosevelt.

Globally the story is the same almost everywhere. Scientists are in lockdown, most staying at home as skeleton crews tend to the most crucial experiments and valuable animal strains. Students and postdocs check in online for group meetings and one-on-one discussions with principal investigators who scramble to amend protocols, decide which experiments and animals to save, and juggle a mass of paperwork and requests from colleges and departments that are charting new regulatory territory themselves. Welcome to the new reality, courtesy of COVID-19. "It is not what we trained for," Tara Spires-Jones, University of Edinburgh, put it mildly.

- With few exceptions, research labs have closed worldwide.
- Most manage to keep essential animal and cell lines viable.
- Scientists fear a long lockdown will set them back years.

For a rare few, lab work goes on as usual for the time being. On March 26 Martin Ingelsson, Uppsala University, Sweden, told Alzforum that his lab was still up and running. "We are encouraging people to work at home, if possible, and we have cancelled group meetings or shifted them online. But most workplaces are open in Sweden," he said. Uppsala University has moved all course work online, but researchers in Ingelsson's lab continue mouse and cell experiments that would be problematic to disrupt. Sweden had 2,840 confirmed COVID-19 cases and 71 deaths as of March 26, according to the Johns Hopkins University of Medicine coronavirus dashboard.

Japan, too, had not enforced lockdowns at time of writing, but Taisuke Tomita, University of Tokyo, told Alzforum that that may be about to change. "The situation in Tokyo is like a rolling stone," he wrote. "We are now facing the possibility of a lockdown," he wrote on March 26. A day later, the university officially locked down, but only until March 30. He expects that might be extended. Tomita oversees international students at his university and has been occupied with travel, class, and scheduling logistics instead of research.

These seem the exceptions to the rule. Most labs are already in some form of mandated lockdown, and for some it came with little warning. "We were taken by surprise," said Bart De Strooper, director of the U.K. Dementia Research Institute. "However, as far as I can tell, most centers responded very well," he told Alzforum. De Strooper's main concern, echoed by the research community as a whole, was for the well-being of researchers, many of whom are now in isolation, often far from home. He also wants precious samples to be saved.

Researchers seem determined to make the best of the situation, yet most fear it will get worse before it gets better. “We hope that we will not get a total shutdown as in Italy,” Christian Haass at Munich’s Ludwig-Maximilians University wrote to Alzforum. “This would be a disaster. Currently, our animal facility is running, and a minimal number of the most important experiments can be finished. This would stop if we get a total shutdown.”

Li-Huei Tsai at Massachusetts Institute of Technology echoed Haass’ concern. “Depending on further policy changes by Massachusetts leaders, at some point we may have to get rid of some mouse strains,” she said. “This would be heartbreaking.” Some strains are on special diets to induce genes or deliver drugs, and their chow was prepared to last a finite time. Should experiments need to be extended because researchers can’t access the labs to analyze the mice at intended time points, that diet could run out. Replenishing it may be impossible because both ordering and receiving have been disrupted. “It is really crazy,” Tsai said. To re-establish those mice could take more than a year, setting experiments back up to two years, she added.

Though Hong Kong was spared from the pandemic compared with mainland China, the logistics problems are similar. “Transportation disruptions, together with the shutdown of companies and research institutes in China, and now the U.S., has had a huge impact on the availability and delivery of supplies and services,” Nancy Ip, Hong Kong University of Science and Technology, told Alzforum. Other labs take heed. Though UST gradually got back to normal after its lockdown started at the end of January, its researchers have just been asked to work from home once again, as a second wave of COVID-19 is gripping the city, Ip told Alzforum.



Lonesome in the Lab. At DZNE’s Biomedical Research Center building near Munich, white window shades open automatically when rooms are occupied (left). On March 25, only two people, Christian Haass and a lab technician, were working. [Courtesy of Christian Haass.]

Investigators have already had to make tough choices. In Edinburgh, Spires-Jones has had to cull some animals and cut other experiments short. “Of course, everyone in the group thinks their experiment is important, but they have been really good about it,” she said. Studies that have been ongoing for years and would be difficult and expensive to do over were given priority.

At Washington University, St. Louis, David Holtzman’s group has managed to continue mouse aging studies, and kill the animals at the appropriate time points and freeze tissue. However, Holtzman said the group can’t do all the planned analyses. Spires-Jones is keeping mice alive to

run behavior experiments at later time points than planned. If the crisis goes on much longer, her group may be denied access to the mice completely, losing the whole experiment and setting her lab back years.

This is a concern for postdocs and students whose careers depend on grants and publications. “We have a lot of experiments that rely on activity recording from fresh tissue slices. They have been lost because use of those lab areas has been restricted,” Lars Ittner at Macquarie University, Sydney, told Alzforum. At the University of Texas Southwestern Medical Center, Dallas, researchers are forbidden from doing “wet” lab experiments, according to Marc Diamond. “Mostly we are fortunate and have been able to freeze cells and keep critical mouse colonies going,” Diamond said. Tsai said that at MIT, most facilities, including cell sorting, sequencing, proteomics, etc., have ceased operation.

Cynthia Lemere at Brigham and Women’s Hospital, Boston, has mice aging right now for a study. She hopes she will be able to get back to them at the required time. Lemere said changes at collaborating facilities can also be catastrophic. She has a grant from NASA to study the effect of deep-space radiation on mice. The study relies on a particle accelerator at Brookhaven National Laboratory, which fires radioactive isotopes at study samples. This week, Brookhaven announced that accelerator beam time schedules for this spring have been postponed, jeopardizing animal experiments that are scheduled for 2021. Some of those animals have already been bred, because they were to be aged to 10 months old.

At many universities, animal facilities are downsizing. At Boston University, researchers have been asked to euthanize as many animals as possible, wrote Carmela Abraham. Staff there have to carry a special document to prove that they are essential personnel, and, as with most institutions, only one or two people per lab can be designated.

Most principal investigators interviewed for this story cannot access their own labs. Personal protection equipment has been reserved for medical staff who are fighting the pandemic. De Strooper said the DRI had donated its masks and other PPEs to Spain, and has assembled a stockpile for use in U.K. hospitals.

In mouse labs, researchers have scrambled to preserve sperm and embryos should colonies be lost. Lemere has 450 cages; she has had to put breeding on hold except for one cage per genotype. “This will limit how quickly we can get mice ready for future experiments,” she said. To prepare for the worst-case scenario, Lemere has shipped mice that can’t be replaced to the Jackson Laboratory, Bar Harbor, Maine, for embryo cryopreservation. Likewise, Spires-Jones has frozen mouse sperm so she can restart some of her colonies should they be lost.

Cell lines, too, have been deep-frozen in liquid nitrogen or -80° C freezers. But not all can be saved. While induced pluripotent stem cells can, differentiated lines may be lost. “This poses a huge problem,” said Haass. While it is still possible at the time of writing to work on these cells at the DZNE, he worries that this may end soon. Chaitra Sathyaprakash, a postdoc in Spires-Jones’ group, had to destroy cortical neuron lines she grew from iPSCs, knocking her work back at least three months. She now worries about whether her funding will continue.

Virtual Reality

On the plus side, researchers have more closely embraced IT. “I have to say I’m more technologically savvy than I used to be,” said Lemere. Lab meetings are going ahead as usual using Zoom, Microsoft Teams, Google Hangouts, and other forms of online communication. Since researchers have found themselves isolated at home, lab journal club has become as much catharsis as a way of learning new science. Some labs hold them daily. Diamond invites other principal investigators to give online presentations to his group. “We will probably just grow that organically to keep people engaged through the science,” he said.

The scientific conference calendar has collapsed. “At least now, nobody can complain about too many meetings,” quipped Haass. Some conferences have been cancelled outright, for example this spring’s Keystone gatherings. Others, such as AAT-AD/PD, have moved to an online format (see Alzforum [conference calendar](#) for regular updates). This is not all bad, some think. “While face-to-face communication is important, maybe we will realize that some meetings are less crucial than we tend to believe,” said De Strooper. “There is often a huge effort to attend, just to catch up on a few new developments, but there are other ways to exchange information,” he said. De Strooper looks forward to AD/PD as a test case, saying, “It will be really interesting to see how that will work.” As of March 23, the Alzheimer’s Association was still planning to hold its International Conference in Amsterdam in July.

Faculty, postdocs, and students are using the time away from the bench to catch up on the literature and to write grants and papers. “I hope some of the most urgent papers in my group will be quickly written, now,” said Haass.

Journals, for the most part, are coping well. Céline Carret, an editor at EMBO Molecular Medicine, said they are operating as usual, if from home. “AD paper authors and referees are as busy as before March, as far as we are concerned,” she wrote. “We are very much focused on continuing to serve science and the scientific community to the best of our ability through this crisis,” wrote Cell Press’s media contact Joseph Caputo to Alzforum. Cell Press have shared the steps it is taking [online](#).

Elena Becker-Barroso, editor at Lancet Neurology, told Alzforum that Elsevier, which owns the Lancet journals, established work-at-home contingency plans for this type of situation years ago, and even carries out “fire drills” from time to time. “Everyone is working at home since March 16,” she said. She thinks review may take a bit longer at some journals because finding peer-reviewers has been more difficult. “We don’t have the hard facts yet because it has been only two weeks since the crisis started, but it is our impression that many reviewers are unavailable because of stress related to clinical commitments,” Becker-Barroso said. Indeed, M.D.–Ph.D. researchers who typically don’t see patients anticipate they may be asked to help out in the clinic. “I may have to brush off my stethoscope, said Marc Aurel Busche, University College London.

The urgency around COVID-19 research has changed publishing priorities. “The Lancet’s journals have seen a significant increase in submissions related to COVID-19, creating unprecedented workloads for editors,” wrote David Collingridge, publishing director at Lancet specialty journals. “We have had to develop new systems of prioritization and workflow, and we are indeed fast-tracking all COVID-19 content considered to be of interest.” “Our ‘fast-track’

maybe is not as fast right now,” said Becker-Barroso about the Lancet’s neurology papers. Even Cell Press has seen its share of coronavirus papers. “There have been a few dozen COVID-19 papers submitted across the Cell Press portfolio, and while we are prioritizing their processing and review, these actions are not taking away from our editors’ abilities to continue as normal,” Caputo wrote to Alzforum.

Some researchers are concerned that papers currently in review, or about to be submitted, may be in jeopardy if reviewers ask for additional experiments that are no longer possible because the opportunity to work in the lab, and/or the necessary study material, have been lost. Tsai is facing just that scenario right now with a paper at Nature Neuroscience. “Reviewers have asked us to do further experiments but I don’t know when we’ll ever be able to do them,” she said. “Journals may have to be a bit more flexible,” she suggested. One journal has advised reviewers to focus on the fundamentals, and if the paper is appropriate and the data sound, to not ask for those “icing on the cake” experiments.

Careers in Limbo

The pandemic will put the careers of young investigators, postdocs, and graduate students on hold. “I feel for the young and younger researchers who work so hard to accumulate data for preliminary results for grant applications and for publications,” wrote Abraham.

Teaching has all but moved entirely online, creating new challenges for faculty and coursework. Some could not access the lecture halls and software that they would normally use to record classes, leaving them to improvise. “The things we take for granted on campus, suddenly become more tricky from home,” noted Ittner.

Some Ph.D. students have already managed to defend their theses online, but for others this has been postponed a month or more, with the potential of further delays if the crises rages on. Tsai said MIT will change to completely virtual examinations, including theses defense. She has two students scheduled to defend in May and June. One had planned for family to attend and wants to postpone in the hope that the lockdown will end.

Young investigators are also affected by the lockdown and the likely hold-up in publishing data. “At the university level, there has been some talk of pausing the tenure clock, wrote Michael Wolfe, University of Kansas, Lawrence.

Postdocs face growing uncertainty. Those on finite contracts worry that paid time will run out before they complete projects. Faculty are optimistic that they can obtain no-cost extensions to grant deadlines, but granting offices are inundated with calls and requests.

Richard Hodes, director of the National Institute on Aging, said the NIA will look at extensions case by case. “If the work simply cannot begin, we would consider delaying the start of funding. It will vary from grant to grant, but we’ll certainly entertain requests to use the flexibility we have to provide extensions in time,” he told Alzforum. “We want to work with the research community to continue our most important mission. We want to hear from researchers about what they’re experiencing and what happens over time, so we can make sure they’re able to

continue or recommence the important research they're doing." The NIH has posted [guidance](#) for grant awardees. Lemere said the Alzheimer's Association will postpone its next cycle of grants, which would normally be adjudicated in June.

New positions will likely be put on hold, as well. Tsai was supposed to have new postdocs start soon, but they will not be able to start on time. "I think very soon we may see a hiring freeze," she said.

This situation is further complicated by visa requirements. Researchers in the United States whose visas are about to expire are unsure what will happen to their status, and no new visas are being issued for people abroad who had planned to come here. "I'm optimistic that, because of the lockdowns and travel restrictions, the government will allow some leeway for people whose visas are about to expire," said Tsai. The visa of one of her postdocs runs out in June. Holtzman said a technician who is essential for animal work is in the same boat. "If we can't update her visa status, I may have to ask her to stop work," he said.

Despite the disruption, researchers are committed to making the best of the situation. They recognize that things could be a lot worse and that losing cell lines or mouse colonies fades relative to the suffering and death going on around them. "These are challenging times. In Roosevelt's famous spirit, we are doing what we can, with what we have, where we are," Wolfe wrote.—Tom Fagan

COMMENTS



Grace Stutzmann

Rosalind Franklin University/The Chicago Medical School

Posted: 27 Mar 2020

The COVID-19 pandemic has thrown quite a wrench in the research works, but we're adapting around it and accepted that some studies will need to be sidelined for a bit. Since Illinois is in a mandatory "shelter in place" order, our university has largely shut down access except for essential personnel, who need to be validated. I have appointed some of my lab members as essential to keep animal lines going and oversee cell lines and equipment.

Now we have no active experiments going on. We're switched more to analysis, writing of papers and grants (I anticipate the NIH will be flooded with grants come June 5 ... which will be a funding disaster with the timing of the government stimulus package ...). As well as online journal clubs and Zoom lab meetings, I'm learning lots about Google hangout as well ... Plus we're at the tail end of the interviewing stage for a new faculty member.

So, we're hanging in there, trying to be creative with how science gets done, and trying to keep to a usual sleep schedule. That been a fail so far.



Michael Wolfe

University of Kansas

Posted: 27 Mar 2020

As of Tuesday, we have had to shut down all lab operations except for those that are essential. For us that would only be ensuring the cryotank with all our cell lines is kept in liquid nitrogen and minus 80 freezers maintain temperature. No experiments have been lost, but they are now on indefinite hold. There was one experiment for which we had data that needed to be readout on Tuesday, and we did complete that.

My lab members are all working from home now. Some of them are writing up manuscripts, but those who do not have manuscripts to write are doing literature searches on specific topics that we hope will refocus our experimental efforts once they can start back up. Some may also write review articles on their topic. We will continue to hold weekly lab meetings by Zoom, with everyone, including me, updating each other on what we learned or accomplished. I am also in touch daily with each lab member individually by email or phone, and I let them all know at the beginning of the day what I plan to do and then again at the end of the day to report progress. We are holding each other accountable to be as productive as possible under the circumstances.



Nancy Ip

Hong Kong University of Science & Technology

Posted: 27 Mar 2020

These are indeed challenging times for all of us.

At the Hong Kong University of Science and Technology, remote work started immediately after Chinese New Year at the end of January. Although research activities on campus gradually returned to normal last week, we were again asked to work from home as the city is potentially facing another wave of the COVID-19 pandemic. As can be expected, the crisis will indeed delay research activities.

It has been challenging to have our entire team working in the lab. Many colleagues who went back home for Chinese New Year had difficulty returning to Hong Kong due to transportation disruptions followed by the requirement to spend 14 days in self-isolation. Such transportation disruptions together with the shutdown of companies and research institutes in China and now the U.S. had a huge impact on the availability and delivery of supplies and services. Our research activities have been interrupted for over two months now, with no end in sight.

Given the utmost importance of unburdening healthcare systems, outpatient services at public hospitals have been terminated or reduced. Therefore, studies involving patient recruitment and sample collection have been postponed.

Nonetheless, we are ensuring that essential activities related to induced pluripotent stem cells (iPSCs) and mouse lines continue. Experiments involving iPSCs require substantial time for cell culture, while mouse lines are precious resources that require continuous, labor-intensive care. Fortunately, a few highly dedicated staff and students are fulfilling these duties to ensure that experiments involving these resources, such as breeding transgenic mouse lines or the differentiation of iPSC-derived neural cells, can immediately start or resume when possible.

In the meantime, we have been focusing on analyzing data and preparing manuscripts. While working remotely, we have been using Zoom videoconferencing to keep regular contact and share updates with our colleagues and also maintain morale despite these current challenges. By reducing in-person activities and focusing on essential lab maintenance, data analysis, and manuscript writing, we hope to resume our normal research activities as soon as possible.



Taisuke Tomita

The University of Tokyo

Posted: 27 Mar 2020

The situation in Japan has changed in the last two weeks. Once a voluntary isolation period ended in mid March, people started gathering outside again, and several restaurants as well as shops opened last weekend. Many Japanese travelers came back from the E.U. and U.S., as the COVID-19 situation was getting worse in these countries.

As a result, the number of patients has significantly increased during this week. Also, several patients with unknown contact history have been identified. We now know that young infected people who do not have any symptoms can spread the virus.

Now, scientists are sending strong warnings about a pandemic in Japan, especially Tokyo and Osaka. In fact, two patients, one a teenager, have been reported in our university. Following how the pandemic situation in the E.U. and U.S. was handled, the administration office of the universities have started to discuss a lockdown and postponement of the new year semester (as you may know, the financial year starts in April in Japan). Today we received an official announcement to lock down the university during (only) this weekend, and they recommend us to stay home. Also, we have already decided to start the year for newcomers from May.

So, while people at the lab worked almost normally until yesterday, now we are discussing how to maintain labs and mouse colonies during a lockdown of the university and the city. Still, we are not under a severe pandemic situation or a collapsed medical care system. But if the patient numbers grow tremendously after next week, the university will probably be locked down. Hopefully the self-quarantine and voluntary refraining for this period prevent further patients in April.

Luckily, lab members are fine. No patient has been identified in our faculty, but the virus definitely comes closer. I think the next two weeks will be critical in determining how this plays out.

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