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ARRIGE NEWSLETTER

Association for Responsible Research and Innovation in Genome Editing

Clinical Applications of Genome Editing

IN THIS ISSUE

EDITORIAL

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President of ARRIGE

Targeting genes for inactivation through standard CRISPR-Cas9 approaches or base editors/editing for correcting mutations appear to be the current and likely future uses of genome editing tools in Biomedicine, both in pre-clinical studies and in clinical trials. These are the current trends, as it can be inferred from most recent publications. They appear to leave aside the original thoughts and schemes where we all anticipated that the homology-driven repairing pathway, with a donor DNA template, would be the way to go. And this is what we all taught our students in our classes and seminars. But, unfortunately, this is not what is happening.

Repairing or introducing mutations triggered by CRISPR-Cas9, in the presence of adequate DNA donor templates, has been explored and applied successfully in many laboratories around the world. These are all academic experiments, using a variety of cells and model organisms, from animals to plants. There is an enormous list of publications documenting such successful genome editing experiments. Most of them have reported minimal efficiencies, when the production of the desired allele is calculated, often hidden among dozens of additional unwanted alleles produced spontaneously by the endogenous cell repairing cascades. However, this pparently limited success can easily be overcome. In animals and plants. Those desired edited alleles with minor representation can be segregated out and efficiently turned into individuals carrying the planned genome edition in the homozygous state through breeding programs. It doesn't matter the characteristic mosaicism of all founder animals or plants obtained with original CRISPR-Cas9 tools. The expected allele can be easily found and brought to homozygosity by subsequent matings.

However, none of the above can be easily transferred to the clinic. We cannot treat patients under the assumption that perhaps one of their children will inherit the corrected genetic modification. This is absurd, it does not work like this in the Hospital and would be ethically unacceptable. Therefore, this was the most obvious Achilles heel for the genome editing field.

Cas9 nuclease is performing excellently in two scenarios: targeting your favorite gene with the help of the corresponding RNA guide and, cutting the targeted gene at predefined locations. The second function can be directly exploited to inactivate genes specifically, aiming for a therapeutic benefit. The first function can be reused by the base (and prime) editor's concept, combined with dead or nickase Cas9 nucleases, targeting another activity to the right place, whether a deaminase or a reverse transcriptase, respectively. There is no need for additional cellular mechanisms. Everything is performed by the CRISPR tool variant.

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Examples for the targeting trend include, already in clinical trials: the inactivation of the BCL11A enhancer resulting in the reactivation of the gamma-globin gene for treating sickle-cell anemia and beta-thalassemia patients; the elimination of an intronic cryptic signal in the CEP290 gene for treating Leber Congenital Amaurosis type-10 patients; the inactivation of the TTR gene for treating transthyretin amyloidosis patients; or the inactivation of PD1 and TCR loci for the innovative immunotherapy for aggressive myeloma, melanoma or sarcoma patients.

On the side of base editors, we have learned in 2021 of the successful correction in mouse models of progeria, an ultrarare disease, and sickle-cell anemia, and, in non-human primates, the successful inactivation of PCSK9 locus resulting in reduced circulating LDL, and hence, cholesterol levels, thereby also reducing the risk for developing atherosclerosis and other cardiovascular diseases, as an example that genome editing tools can also be applied to common and complex diseases. Having presented the current trends in Biomedicine for genome editing tools, the principle of justice remains primordial. In particular, we have yet to solve how we are going to bring all these innovative therapeutical advances to all the patients suffering from life-threatening diseases such as sickle-cell anemia or beta-thalassemia. Victoria Gray was the first patient to be cured in the U.S.A., but millions exist in South America, Africa and Asia who cannot afford spending the sums that most likely will be the price to pay for accessing these novel treatments. Hence, ARRIGE's acknowledges and celebrates these technical advances but we also raise our voice demanding a sincere debate about universal access to these technologies.

ARTICLES

Human Genome Editing Enters the Reproductive Clinic

S. Eben Kirskey, Ph.D., Anthropologist, Associate Professor, Alfred Deakin Institute, Australia

Ideas about eugenics, or "good genes," have a long legacy. In studying the world's first clinical applications of CRISPR gene editing as a cultural anthropologist, I was particularly interested in how eugenic ideas are playing out in the field of reproductive medicine. My book, The Mutant Project (2020), is a close study of the different values that came together in the laboratory of Dr. Jiankui He who produced the world's first "edited" babies in Shenzhen, China. In this city that is known for speed and innovation many different values—related market speculation, scientific progress, national glory, as well as ethical calculations about the health and well-being of marginalized peoples—shaped the selection of a good genetic target for the world's first experiment with CRISPR in human reproductive medicine.

The laboratory of Dr. He decided to "delete" a single gene in human embryos: a receptor called CCR5 that is a port of entry for the HIV virus into cells. By knocking out the CCR5 receptor, Dr. He hoped to create babies that were resistant to viral infections. Some people are already resistant to HIV since they were born with mutation to this receptor that is called CCR5-Δ32. Rather than copy and paste this "good gene" into human embryos, Dr. He actually used CRISPR to scramble the genetic instructions for the CCR5 receptor, which he saw as a bad gene. Each of the human embryos in the study had an idiosyncratic pattern of damage.

Initially, Jiankui He's laboratory was conducting research on another gene, called PCSK9, associated with high cholesterol. The CCR5 receptor was targeted only after a Communist Party official introduced Dr. He to impoverished HIV patients who were living with discrimination and inequality. People who are infected with HIV in China, and other places like Europe and the United States, have a life expectancy that is very similar to normal. Existing life-saving medicines, that protect people from this virus, are already widely available in these jurisdictions. Jiankui He sought a high-powered technological fix to social problems.

While there was much controversy about Dr. He's experiment, all of the initial public reports missed a very consequential fact. The twins that resulted from the study, nicknamed Lulu and Nana, were born with some serious health problems. In my book I report about how the babies were in a neonatal intensive care unit (NICU) when Dr. He recorded a video for YouTube claiming they were as healthy as any other newborns. I have considered evidence that these health problems are a result of known risks of IVF and twin births, or unknown problems introduced by the CRISPR experiment.

Dr. He failed to conduct some basic science after the birth of these babies. The laboratory did not definitively determine if their cells were in fact resistant to HIV. Instead of staying focused on a rigorous program of research, he was travelling with some of his collaborators to explore potential business ventures. He was working to set up a major clinical institute in Hainan—an island off the coast of southern China that has been designated a special zone for medical tourism and experimentation. In Bangkok he met with executives with Steve's Fertility Clinic—a facility where he also conducted implantations of human embryos that had been modified with CRISPR.

At this point it is still difficult to assess if the gene for the CCR5 receptor is a "good gene" or a "bad gene." Genes exist in cells and bodies that live within shifting ecological and historical conditions. While deleting this particular gene may protect people from HIV infections, lacking this gene may inadvertently make people vulnerable to other diseases. While market forces continue to propel eugenic dreams into the reproductive clinic, there is still no consensus about which "good genes" should actually be passed along to future human children.

From Gene Knockout to Gene Repair

André Choulika Ph.D., CEO of Cellectis

In June 2015, the first-ever therapeutic success of a gene edited product was conducted with the goal of treating an aggressive leukemia on a patient, Layla Richards, a 9-month-old girl who had run out of options for treatment*.

For the first time in medical history, gene editing came to the forefront as a tool that delivers on the concept of altering the genes of allogeneic T-cells to treat aggressive forms of cancer.

This first successful treatment revitalized the conversation within the scientific community on how to use gene editing to treat patients with high unmet medical needs: the **gene knockout** i.e., disabling a gene in a cell.

Gene Knockout

The goal of introducing these edits is to induce a loss of function for the cells for a potential therapeutic application. Regarding the knockout cited in the CAR-T cell therapy mentioned above, the TCR-alpha and CD52 genes were disabled to respectively suppress the natural alloreactivity of T cells (GvHD) and sensitivity to an anti-CD52 monoclonal antibody (to prevent Host versus Graft rejection). Since then, many other knockouts have been performed where T cells lose other functions such as B2M or PD1.

An additional example is the knockout of the BCL11A gene coding for the repressor of fetal hemoglobin (HbF) in hematopoietic stem cells (HSC) allows to compensate the sickled hemoglobin (HbS) in sickle cell disease and beta Thalassemia although mutated hemoglobin remains present in cells. In addition, recent advances in in vivo gene editing to treat transthyretin (ATTR) amyloidosis is also made by a knockout of the TTR gene in liver cells to shut down the production of misfolded transthyretin (TTR) protein.

Therapeutic gene editing has always been associated with "fixing" a specific gene causing a disease instead of knocking it out. To validate this approach, all patients who have been treated with a gene edited product, have received treatments that were previously edited via gene knockout. Though knockout strategy remains effective, many patients around the world are suffering with debilitating/chronic genetic diseases such as Sickle Cell Disease Cystic Fibrosis or Duchenne Muscular Dystrophy for which gene knockout strategy will not work.

If this is the case, why do all initial therapeutic approaches utilize gene knockouts while a true gene repair would free patients from mutations causing their disease?

Gene Repair

The second stage of gene editing development is the *ex vivo* **gene repair**. In comparison to **gene knockout** this process adds a new dimension of complexity within the field of therapeutic gene editing.

*Treatment was completed at the Great Ormond Street Hospital in London in the UK

To repair a mutation in a gene you must:

- Precisely target the debilitating mutation
- Remove the mutation
- Rewrite the gene to render it functional.

This process must be efficiently performed in enough cells to result in therapeutic effect. Ex vivo gene repair, most frequently applied to **Hematopoietic Stem Cells** (HSCs), is a powerful first step to seek cures for patients with previously uncurable genetic diseases. It is also a cautious approach towards a better understanding of the power, limitations and risks of gene repair. Sickle Cell Disease (SCD) will likely be one of the first genetic diseases to be "treated" by gene repair, as it combines two main advantages:

- Potential to benefit many patients across the world with high unmet medical need
- The feasibility of using an ex vivo approach for gene repair Bringing all the material into the same cell (to operate a gene repair) is less complex and more controllable ex vivo than in vivo, as you have to achieve a proper balance between the nuclease (Crispr, TALEN or others), the DNA repair matrix and potentially other reagents to control DNA repair pathways.

Most importantly, an ex vivo approach allows for greater post-editing control, meaning you can verify what has happened in the edited cell. For instance; you can see what percentage of cells have an accurate repair versus cells that have either not been modified or where unwitting modification have occurred? Is there off target cleavage or chromosomal re-arrangement such as unperfect recombination, chromosomal deletions or translocations? Therefore, as a first step, a deep investigation of all events that have occurred in the pool of cells receiving the editing therapy is crucial.

Gene repair is a complex mechanism and its success relies on many factors. A simple parameter is the position of the cleavage site compared to the mutation to be corrected. The closer the proximity that the cut is placed onto the mutation the higher the efficiency will be. Gene conversion (extension of the DNA tracks upstream and downstream the mutation) will diminish as the distance increases from the place of the cut to the place of the edit.

The balance in the speed of release of the nuclease from the DNA post cleavage is of paramount importance for the success of safe gene repair. If the nuclease releases one tip of the DNA faster than the other, it will allow the entry of exonucleases 5'-to-3' and the recombinogenic 3' protruding single stranded DNA tip that will look to be repaired while the other tip is still bound to the nuclease. This unbalance is nuclease dependent and could be one of the main factors of inaccurate gene repair. Dissociation constant (Kd) of each nuclease must be measured on each side of DNA tips post cleavage and closely monitored to limit differential releases of each tip. The slow-to-be-released tip could have a strong impact on gene repair outcome and at worst could lead to a one-sided recombination, translocation or even chemothripsis.

Ex vivo gene repair has the potential to be a powerful platform to treat many diseases, but is also an approach that will provide a better understanding of the power, limitations and risks of gene editing. In vivo gene repair is poised to become the next wave of innovation in gene editing.

Recent Advances on Nonviral CRISPR Nanoformulations for Brain Delivery and Clinical Approaches

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CRISPR-Nonviral nanoformulations for brain delivery

CRISPR is being increasingly used in neuroscience, particularly to advance research on neurodegenerative diseases. Although, the blood-brain barrier (BBB) limits the penetration of most therapeutic compounds making drug delivery to the brain a major clinical challenge. Despite the broad range of applications of the CRISPR/Cas9 system in the context of the brain, the efficient delivery of the CRISPR/Cas9 remains a key limiting factor. The CRISPR/Cas9 can be delivered in different forms like DNA, messenger RNA (Cas9 mRNA), Cas9 ribonucleoprotein (RNP) complex (Cas9:gRNA complex) and donor DNA. The strategies used for brain delivery of the CRISPR/Cas9 system are principally divided in viral and nonviral vectors. Compared to viral approaches, nonviral nanoformulations offer greater control over how long the components remain in the cells whilst reducing off-target effects and toxicity in the brain. Besides that, nonviral approaches have several advantages such as minimal immunogenicity, low production costs, possibility for large scale production, the ability to deliver all components of a CRISPR-Cas9 system within one vector (all-in-one delivery), and the safety and flexibility to deliver various cargoes.

The principles used for the preparation of the nonviral formulations should take in consideration the selection of the CRISPR/Cas system components, biocompatibility, strategies to facilitate the cellular internalization of the formulation and the safety. Some studies indicate that NP with RNPs can be deliver in the mouse brain without activating the microglia in the central nervous system immune cells **(1)** showing the safety of the formulation. In addition, although some formulations tested so far in the context of the brain showed higher preference to neurons rather than astrocytes **(1)**, the control of gene editing in specific brain cell populations remains to be demonstrated. Another issue that remains to be investigated is whether the nonviral formulations can be administered by intravenous route and accumulate in the brain. This strategy could simplify enormously the deployment of gene editing formulations for brain applications. However, failure to conduct precise gene editing in brain cells within a certain time may result in undesirable consequences, such as serious off-target effects, representing a critical challenge for the clinical translation of the technology. Recently, some emerging strategies using genetic regulation, chemical and physical strategies to regulate the activity of CRISPR/Cas9 have shown promising results in the improvement of spatiotemporal controllability. For example, it was shown that a non-invasive, magnetically-guided NP containing a CRISPR/Cas9 plasmid was able to cross the in vitro BBB model and inhibit latent HIV-1 infection in microglial cells **(2)**.

Some strategies show some promising preclinical results, still some concerns must be addressed in the future: (i) higher packaging capacity of the RNPs; (ii) specificity -innovative nonviral nanoformulations that can distinguish diseased cells from the healthy cells in clinical trials to reduce off-target effects are needed; and (iii) the development of new nanoformulations that can respond to multiple stimuli in target cells in another direction to explore.

Clinical trials

The list of diseases potentially treatable using CRISPR-based technologies has been growing every day. The data from clinical trials released recently has demonstrated that CRISPR therapy can treat several genetic diseases ranging from blood diseases like sickle cell anemia to cancer **(3)**.

Currently, clinicaltrials.gov has eight completed, active, or recruiting trials involving CRISPR. Besides its use in diagnostic, CRISPR has triggered attention as a potential therapeutic tool.

There are >25 completed, active, or recruiting trials across the globe using CRISPR technology for ex-vivo gene editing prior to autologous or allogeneic administration to patients. The ex-vivo CRISPR-based immunotherapies primarily utilize chimeric antigen receptor (CAR) T-cells or modified T-cell receptor (TCR) therapy **(4)**. Besides that, only 10% of clinical trials conducted so far employed nonviral methods.

Clinical trial NCT03872479 that began in September 2019 and it is the first of its kind to use an in vivo CRISPR therapeutic. The objective of the trial is to evaluate the safety, tolerability, and efficacy of ascending doses of subretinal injections of EDIT-101 (AAV5 viral vector carrying SaCas9 and two highly specific sgRNAs) in patients with Leber Congenital Amaurosis Type 10 (LCA10) **(5)**. LCA10 is characterized by severe cone-rod dystrophy and poor vision. This rare condition is caused by an autosomal recessive condition due to an IVS26 point mutation (c.2991 + 1655 A > G) within intron 26 of the CEP290 gene, resulting in a splicing defect leading to the appearance of an early stop codon within the mRNA. EDIT-101 was designed to restore the full-length mRNA and protein via deletion or inversion of intron 26. In preclinical studies using mice and non-human primates, EDIT-101 was well tolerated and showed sufficient editing efficiency for vision restoration, since as little as 10% functional foveal cone photoreceptors are sufficient for near-normal vision **(6)**.

In November 2020, two new in vivo trials began. The first trial (NCT04560790) aimed to test the safety, tolerability, and efficacy of single escalating doses of BD111 as a therapy for herpetic stromal keratitis caused by Herpes simplex virus type I (HSV-1) **(5)**. This gene editing therapy introduces BD111 CRISPR/Cas9 mRNA for the treatment of refractory herpetic viral keratitis to prevent infectious blindness in those patients. The second trial (NCT04601051) is for the treatment of hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) **(5)**. Hereditary ATTR is caused by mutations within the TTR gene that result in misfolding of the protein transthyretin (TTR). The misfolded TTR aggregates into amyloid fibrils in various organs resulting in organ dysfunction. NTLA-2001 consists of Cas9 mRNA and sgRNA delivered intravenously by lipid nanoparticles making it the first in vivo CRISPR therapy to be systemically administered **(7)**. As a Phase 1 trial, the aim is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of NTLA-2001 in ATTRv-PN patients to determine the optimal biologically active dose.

The current trials using CRISPR-based treatments are still in early stages and until now non study for neurogenerative diseases using non-viral CRISPR formulations are in clinical trials. That means that even if the technologies are effective in pre-clinical studies, they are likely still a few years away from to patients. Some steps in early trials need to be address like the targeting, side effects, safety, and later trials test efficacy and compare new therapies with standard treatments.

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FREE COMMENTARIES

Genome Editing: Global Governance

Alta Charo, Member of the WHO Expert Committee on Developing Global Standards for Governance of Human Genome Editing, Warren P. Knowles Emerita Professor of Law and Bioethics at the University of Wisconsin, U.S.

In Hong Kong, at the November 2017 International Summit on Human Genome Editing, a shocking announcement fired a starting gun on global governance for this emerging technology. The editing of embryos, resulting in two live births, represented the first known – and to date, the only known – example of clinical use of heritable human germline editing. The fact that the work was done without sufficient justification, without sufficient pre-clinical research, without sufficient oversight, without the fully informed and voluntary consent of the parents and, at the end of the day, without the intended results all led to a clamor for a more robust global governance framework.

Two international efforts emerged from these events.

The first was a focused study of heritable germline editing. Convened by the U.K. Royal Society, U.S. National Academy of Medicine, and the U.S. National Academy of Sciences, with participation from academies of sciences and medicine from around the world, the "International Commission" evaluated potential clinical applications of human germline genome editing, and the preclinical science needed to make it safe and effective enough to use if any society concluded that such uses were politically and culturally acceptable.

The second was a broader study of both heritable and non-heritable forms of human genome editing. In December 2018, WHO established a global, multidisciplinary "Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing" to examine the scientific, ethical, social, and legal challenges associated with human genome editing and to develop a framework to help national governments develop and implement their own policies.

The WHO issued two reports, one on a governance framework and another with specific recommendations. Together the two publications provide advice and recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing.

A key consideration for the WHO Committee was the diversity of attitudes among individuals and among societies regarding various applications of genome editing, with heritable germline editing the subject of the most profound debate. While treaties and conventions are a tool for global governance, they are challenging to develop and enforce. Therefore, in addition to such approaches, the WHO Committee looked at opportunities to use regional agreements, national regulators, professional societies, national academies of medicine, and civil societies to develop norms and processes that reflect local values. A key goal was to ensure that national policies can be coordinated, even if they cannot be harmonized.

The WHO Committee also recognized that governance in this area must reflect the key characteristics of an emerging technology: rapidly advancing scientific understanding, expanding areas of application, evolving tools and approaches for risk evaluation and mitigation measures, and lack of historical data on dissemination patterns and effects on the general public. The Committee therefore stressed that good governance is an iterative, ongoing process that includes mechanisms for regular revision. Ideally, it is proactive, not only reactive. It requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public. It promotes public confidence.

The report identifies the values and principles that must underlie good governance of emerging technologies, including genome editing. As to how governance tools and programs are made, the Committee emphasized:

(i) openness, transparency, honesty and accountability;
(ii) responsible regulatory stewardship;
(iii) responsible stewardship of science and
(iv) responsible stewardship of research resources.

As to what those tools and programs should be, the Committee emphasized the following:

(i) inclusiveness;
(ii) caution;
(iii) fairness;
(iv) social justice;
(v) non-discrimination;
(vi) equal moral worth;
(vii) respect for persons;
(viii) solidarity; and
(ix) global health justice.

Because it looked at a broader set of uses than the International Commission, the WHO Committee identified different major concerns depending upon the particular application. The report contains a series of questions focused on issues specific to each application of genome editing, and are designed to be a guide when nations decide to set their own policy.

For somatic editing, already the focus of clinical trials for things such as sickle cell anemia and certain forms of blindness, the Committee identified three key issues. The first concerned respect for persons, and focused on avoiding what some have called “ethics dumping,” i.e. moving clinical research to under-regulated areas to avoid costly and time-consuming rules that exist in well-regulated countries, with the intent of using the data to obtain marketing approvals in higher-income countries. The second concerned global health justice and solidarity. If these therapies are developed in a manner that makes them too expensive or too logistically challenging for lower-resourced countries, then the benefits of the technology cannot inure to the global population. Sickle cell treatments, for example, are currently being tested using in vitro editing, but global access may depend upon developing in vivo methods better suited to some regions.Responsible stewardship of the technology means anticipating these equity issues and developing strategies early on to address them, whether through financial or technological innovation.A third concern focused on caution.Experience with stem cell therapies demonstrated the risk of misguided medical tourism, in which fraudulent, premature or even dangerous interventions are promoted in under-regulated areas and tempt people to travel for therapies that are not proven and possible unsafe.This may not only occur for “therapeutic” interventions, which tempt those who are desperate, but also for so-called “enhancements” that are unlikely to be approvable at this time due to the unreasonable ratio of risk to possible benefit.

The WHO report also discusses the use of somatic editing in utero. Fetal surgery has been in clinical practice for many years, and fetal gene therapy is now an active area of inquiry. When exploring the possibilities in the future for treating a fetus in utero with genome editing, complexities multiply due to the need to attend to the health of the pregnant woman, as well as to the risks of unintended effects on the fetus, including unintentional germline alteration. Because laws governing abortion vary so much from country to country, in utero editing also would require careful attention to what is allowed in the event of a problem and, in the case of countries with few abortion options, would also require attention to the permissibility of traveling outside the jurisdiction for service.

Epigenomic editing was also addressed in the WHO report, largely to highlight the importance of ensuring that regulatory approaches properly account for possibly transient or reversible effects, thus altering evaluation of both risks and possible benefits. Epigenomic editing might also be an area in which so-called “enhancements” are most tempting, and policies must once again determine how to define ‘enhancement’ and whether to manage it differently than prevention or therapy.

Looking at heritable germline editing, the WHO Committee built on the International Commission report, but did not choose to draw conclusions about whether it could ever have applications that justify its risks, leaving that to national regulators.But the Committee did highlight the need to manage cross-border concerns if the technology becomes available anywhere. In addition, the Committee called for far more transparency about the preclinical work related to heritable germline editing, and it is looking to expand existing registries of somatic editing clinical trials in order to capture some of the preclinical work, so that the world is never again caught off guard, as it was in Hong Kong. The Committee also outlined a system by which those who believe they have discovered unethical or illegal work can send information to a hub at WHO, which in turn would identify the governmental or professional or other body best positioned to investigate and, if necessary, to take action.

The emphasis on transparency and inclusion was reflected in how the Committee did its work. To ensure a participatory process, the WHO Committee consulted with international and regional organizations, national regulatory authorities and research institutes, patient groups, civil society organizations, indigenous groups, industry associations, private companies, national academies, professional societies and other interested parties. The Committee also held two in-person and 15 online topic-specific meetings drawing on contributions from 71 distinct groups.

Overall, the WHO Committee worked to identify overarching values in how to approach this emerging technology, and then laid out a series of questions that national regulators and policymakers should consider when choosing how to govern its applications. It used scenarios, from realistic to speculative, to demonstrate how different approaches might play out. And while it recommended continued leadership on this topic from WHO, it also worked to provide guidance for policymaking at the national level.

CRI, a New Host for ARRIGE

Ariel Lindner, CRI Co-founder and research director
Dusan Misevic, CRI Director of Research Affairs

As of this year ARRIGE is hosted at CRI, https://www.cri-paris.org, an interdisciplinary learning and research institute located at the center of Paris. The CRI acronym can be interpreted as Center for Research and Interdisciplinarity, but also as Carrefour de Rencontres Intéressantes, a “Crossroads of Interesting Encounters", highlighting not only the interdisciplinarity but the focus on interactions between all the actors assembled at CRI. At its new building located in the heart of Paris Marais district, CRI has built a middleground, an intermediary space that is catalyzing interactions between institutions (Uppergrounds) and innovative individuals who are looking for new ways and who may feel isolated or even marginalized (Undergrounds).

The main mission of CRI is co-constructing and sharing new ways of learning, teaching, researching and mobilizing collective intelligence in the fields of life, learning and digital sciences, in order to face the world's sustainable development goals (SDGs). CRI’s strong learning component promotes innovative pedagogy by putting the students at the heart of their own learning through research educational experience in various programs, from pre-school to PhD including lifelong learning, together with Université de Paris. With Université de Paris, CRI also co-founded the interdisciplinary action-based research challenge institute (“Institut des Défis”) to prototype a model of a Learning University. On a global education stage, CRI hosted World Innovation Summit for Education in Paris (WISE@Paris) and the first edition of the #LearningPlanet Assembly in partnership with AFD (French Agency for Development) and UNESCO.

In terms of research, within its INSERM-Université de Paris research Collaboratory Unit (UMR1284, https://research.cri-paris.org/), CRI aims at transcending barriers between disciplines, science and the society by facilitating the transition from closed scientific inquiry to an open science model.CRI fosters research at crossroads between interdisciplinary life and health sciences, basic understanding of learning processes and novel education technology/methodology testing and implementation, and digital sciences. CRI researchers pursue research projects to tackle the world’s health and education challenges focusing on:

(1) Open health: from data-rich research to development of frugal software and hardware solutions, (2) Open learning: from understanding learning to human-machine paradigms, (3) Open AI: Understanding and shaping current digital transition in context of learning, health and/or human-machine paradigms, (4) Open phronesis: tackling ethical challenges of our time, and (5) Open synthetic and systems biology: from foundational understanding of living systems to open biotech and open pharma solutions. CRI strongly believes these topics are among those most amenable to bridge foundational research and societal impact, and they certainly include genome editing, which is an integral part of a number of research projects currently being developed at CRI.

CRI was founded by François Taddei and Ariel Lindner in 2006 to create an open environment where students, partners and researchers can collaborate together to build a world where lifelong learning is at the heart of our society. Over the past 15 years the CRI community has grown to currently include over 40 researchers, 350 students and 1300 alumni. This has been possible in large part due to the strategic long-term partnership with the Bettencourt Schueller Foundation. Additionally, CRI is supported by a wide range of partners as Ville de Paris and is supported by grants from Axa Foundation, European Union, les Programmes d'investissements d'avenir (Future investment programs), Agence National de la Recherche (French National Research Agency), MSD Avenir.

The synergies between goals, missions, and approaches of ARRIGE and CRI are many and easily evident. For example, in 2017 CRI brought together many international experts for the advanced workshop on Future Paths of Synthetic Biology. The summary notes of the workshop concluded with the recognition of arising social and ethical risks in the field and a call to solve them in an open science spirit, with a knowledgeable public as partner. That type of ethical considerations, and responsible research and innovation in general, are indeed central to the mission of ARRIGE, and partnership with CRI effectively advances towards it.

Open Science in general is a major domain where CRI and ARRIGE can fruitfully interact. The CRI promotes and develops Open Science methods and culture that fosters collaboration between researchers, interdisciplinarity and the engagement of other stakeholders (patients, learners, citizens etc.). Open science creates transparency, which facilitates reproducibility, and trust in results, researchers and institutions. In recent years, Open Science has lowered the barriers to the flow of information between scientists. CRI has repeatedly encouraged, through citizen science, public participation in the scientific process, and included it into educational programs though Open Science courses. These approaches line up perfectly with the ARRIGE objective of both advancing societal scientific, ethical, social, legal and political reflection in the field of genome editing and the dissemination of reliable, trusted information. CRI strongly believes that the future of science must be open, and wishes to jointly work on this goal with ARRIGE in the domain of genome editing.

Furthermore, as of last year, CRI is also hosting the International Genetically Engineered Machine (iGEM) Foundation - an independent, non-profit organization dedicated to the advancement of synthetic biology, education and competition, and the development of an open community and collaboration. iGEM's biggest program is the iGEM Competition, during which multidisciplinary university student teams work together to design, build, test, and measure a synthetic system of their own design using interchangeable biological parts and standard molecular biology techniques. Every year nearly 5,000 people dedicate their summer to iGEM and then come together in the fall to present their work and compete at the annual Jamboree which will be held in Paris in 2022. Connecting iGEM in ARRIGE networks would benefit both organizations and having them co-hosted at CRI is a great first step towards a long term meaningful collaboration.

In constructing a middleground, CRI is bringing together many different stakeholders, including academics, researchers, clinicians, public institutions, private companies, non-governmental organizations, regulators, citizens, governmental agencies and decision makers, across a variety of topics, including synthetic biology and genome editing. This is exactly the type of community ARRIGE is targeting in order to construct the global governance of genome editing. CRI is excited to have ARRIGE as part of its global network of partners, as well as to create stronger connections with the diverse and exciting group of stakeholders assembled in ARRIGE.

COMMUNITY NEWS AND CONTRIBUTIONS

Recent Publications

- Soni, S. The Brave New World: should we tread down the path to human germline editing? South African Journal of Bioethics and Law 15(1) 24-29 (2021) (DOI:10.7196/SAJBL.2021.v14i1.00713)
- Soni, S. WHO guidelines on human genome editing: why countries need to follow them. The Conversation August (2021) (https://theconversation.com/who-guidelines-on-human-genome-editing-why-countries-need-to-follow-them-164895)
- Thaldar D, Townsend B, Botes M, et al. A virtual deliberative public engagement study on heritable genome editing among South Africans: Study protocol. PLOS ONE 2021; 16:e0256097 (doi:10.1371/journal.pone.0256097)
- Feeney O, Cockbain J and Sterckx S (2021) Ethics, Patents and Genome Editing: A Critical Assessment of Three Options of Technology Governance. Front. Polit. Sci. 3:731505. (https://doi.org/10.3389/fpos.2021.731505)
- Feeney, O., & Rakić, V. (2021) Genome editing and 'disenhancement': Considerations on issues of non-identity and genetic pluralism. Humanit Soc Sci Commun 8, 116. (https://doi.org/10.1057/s41599-021-00795-w)

Webinars

An ethics-focused virtual panel series was developed through a collaboration between McMaster University's Institute on Ethics & Policy for Innovation (IEPI) and FNIH GeneConvene Global Collaborative, and produced through the Gene Drive Research Forum:

- Is there a moral difference between the natural and synthetic? July 13, 2021; Moderator: Fredros Okumu, Ph.D., Ifakara Health Institute: https://www.youtube.com/watch?v=_GovnohWGgY
- Do justice and equity concerns bolster or hinder the case for the use of gene drive applications? August 10, 2021; Moderator: Sam Weiss Evans, D.Phil., Harvard University: https://www.youtube.com/watch?v=lXvl6cEWmbU
- Who owes what to whom: What is the nature and scope of responsibilities of the various actors in gene drive research? September 14, 2021; Moderator: Jim Lavery, Ph.D., Emory University: https://www.youtube.com/watch?v=OCZQQ6U61QY
- From principles to principled action: What ethical principles ought to govern gene drive research? October 12; Moderator: Katherine Littler, W.H.O.: https://www.youtube.com/watch?v=5tPnIOEXw4M
- Does gene drive raise exceptionnal ethical issues ? November 9, 2021; Moderator: Claudia Emerson, McMaster University; registration at fnih.org/Unsettledethicalissues

Editorial committee: M. Abecassis, H. Chneiweiss, F. Hirsch, L. Montoliu

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ARRIGE Board Elections Results

ARRIGE Elections Committee announced on October 25th, 2021 the results of the ARRIGE Board Election for the **2022-2024 mandate**.

The nine candidates who received the most votes from ARRIGE Members are the following:

Lluís Montoliu
Hervé Chneiweiss
François Hirsch
Jennifer Merchant
Christine Lemaitre
Bonginkosi Shozi
Sheetal Soni
Cyril Sarrauste de Menthière
Julian Kinderlerer

ARRIGE Newly-Elected Board will officially take office following the next **General Assembly**. Information will follow shortly.

Thank you to all ARRIGE Members for their continued involvement and support. Congratulations to the candidates and the Newly-Elected Board Members!

More information available at https://arrige.org/

You can register to ARRIGE here

Editorial committee: M. Abecassis, H. Chneiweiss, F. Hirsch, L. Montoliu

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