Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Highlight

Contagion 2.0☆

Vaccination is probably Medicine's greatest success story up to date [2].

Smallpox has definitively been eradicated in 1980, poliomyelitis is close to extirpation, measles, pertussis or tetanus are widely controlled [3]. Vaccines comprise an arsenal of dead and mutated specimens, pieces and secretions, synthetic peptides and chimaeras, all of them dispensing acquired immunity to a specific disease.

Live attenuated vaccines, in particular, miming best the "natural" infection, hold the advantage of eliciting the most complete and long-lasting immunization, are relatively inexpensive to produce, suitable to be distributed to large populations and do not require adjuvants. Random chemical mutagenesis has given way to site-directed genetic engineering and multiple licensed vaccines for bacterial and viral pathogens [4].

Vaccination is a fascinating performance.

It is the interplay between the immune system and the invading pathogens, mobilizing in turns hordes of specialized cell populations, shaped and tuned by eras of co-evolution. But as expected from any highly complex, multi-leveled system, it is not entirely predictable. The work of Yanfen Ma and colleagues in this issue prove how unforeseeable the genetic manipulation of the pathogen can be, where the simple insertion of a transgene produces an attenuated strain even in the absence of triggering the intended suicide mechanism [1]. Vaccination started long before the molecular details behind infection, contagion and immunity were elucidated, and vaccine production has partially stayed a carefully supervised empirical science. Several attenuated strains used for vaccination arose by chance over passages, while the very necessity to maintain and amplify the strains requires further passaging, rendering vaccine production also a major logistic challenge, in order to assure the safety, quality and homogeneity of products over the world, including the panoply of issues linked to the preservation, transport and administration of the vaccines [3].

Vaccination is an economic and political issue.

Currently, South Korea and China are in the grip of the largest outbreak of MERS (Middle East respiratory syndrome) since the first reports of the virus in 2012, a virus with high structural similarity to the SARS coronavirus (severe acute respiratory syndrome), which infected 8273 and killed 700 people in 2002/2003. MERS originated in bats, uses camels and dromedaries as an animal reservoir, can be transmitted from human to human and elicits respiratory distress plus multiorgan failure in its victims, with a fatality rate of about 35% [5]. However, despite the repeated call from scientists and several valuable discoveries which could probably be transformed into treatments and vaccines [6], the pharmaceutical companies showed limited interest in investing into MERS, as the disease kept a relatively low profile over the past three years and numerous other catastrophes fought simultaneously for economic and media attention.

Now, at the time of mid-June, MERS accounts for 162 cases of infection, 19 casualties and over 6000 quarantined people and the need for efficient countermeasures urges [7]. Yet the epidemics market is unpredictable and the career of an average health minister can be endangered as much by prudence and vaccine stockpiling as by negligence.

Vaccination is a sociological issue.

Individual freedom and rights come across social responsibility and civic duty [8]. As vaccination works by herd immunity to dyke up the spread of infectious pathogens, it requires a vast majority of individuals to conform to mandatory vaccination, notably members of specific professions such as health care workers [9]. However, the mentality of the modern Western world has shifted to the worship of the individual, asserting round the clock that it is the duty of society to insure its unconditional well-being, and not that it might be the individual's duty to ensure the society's well-being. Accepting a minor risk at the individual level in order to decrease the risk at the group level has become way less self-evident for a generation that has never witnessed the real ravages of vaccine-preventable diseases but is rather obsessed with the precise caloric content of 100% organic quinoa instead. Moreover, personal exemptions from mandatory vaccination are often allowed – 48 states of the USA give leave to religious and 15 to philosophical exemptions, whatsoever the precise definition of the latter might be [H]. Yet,

☆ Article highlight based on "Inducible suicide vector systems for *Trypanosoma cruzi*" by Yanfen Ma et al. [1].

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studies show that outbreaks of measles and pertussis correlate with higher numbers of exemptors and anti-vaccine movements [8].

And finally, vaccination is the sad occasion to study the spread of a novel, extremely virulent and contagious disease [10].

The one of misinformation, fear and doubt, *via* a medium a thousand times more efficient then the release of an influenza virus in the middle of Woodstock – the Internet. The global reach and instantaneous nature of virtual information has rendered harmless neighborhood rumor spreading a dangerous and powerful tool with a major sociological and political impact [11]. Scientists might roll their eyes over ten thousands of "likes" of a webpage claiming that vaccines cause homosexuality and tear one's hair because of Andrew Wakenfields fraudulent research linking MMR vaccine to autism and the ensuing "overnight autism" stories. Once anti-vaccine forums appear in the vicinity of the Centers for Disease Control (CDC) upon online research for "vaccines", leading to noticeable vaccine refusal, delayed vaccine schedules, measles being declared endemic in the UK and diphtheria cases in Spain however, the alarm bell should ring. Moreover, while the veracity of the content of any account, preferentially emphasized by horrifying pictures, is not put to the test, the tool that is meant to democratically make information available to everyone is ironically a hotspot of censorship - the content of many fervid anti-vaccine sites is tightly controlled and any comment relating a deviant view is immediately removed [12].

Partially due to a hint of snobbism, the scientific and medical community is running behind in the world of Web 2.0. Neither do sober statistics and evidence-based information written in technical jargon have the same appeal as emotion-driven horror stories, nor does an equivalent in form of pro-vaccine narratives and listings of uneventful vaccinations exist [12]. Studies have shown that the tone and nature of comments published alongside a neutral article presenting a new technology significantly skew the reader's interpretation of risks associated with the latter, way more than the effective article content, demonstrating how easily the average internet user is manipulated by his peers [11]. As long as no vaccine has been developed against the propagation of myths and conspiracies, the scientific world should better speed up its domestication of social media in order to re-establish a correct perception of the risk-benefit output of vaccines.

As for the alternative solutions, web cartoonist and ex-NASA roboticist Randall Munroe, furnishing "serious scientific answers to absurd hypothetical questions" *via* his "What if?" blog [13], has addressed the issue if common cold (i.e. rhinoviruses) could be eradicated by all individuals of the planet keeping the maximal possible distance from each other (i.e. about 77 m) for a couple of weeks. Apart from not working, due to reservoirs in for example immunocompromised persons, this would probably cause the breakdown of global economics [14].

1. Biosketch – Dr. Huan Huang

Huan Huang holds both a degree of Medicine as well as of Molecular Biology and Biochemistry. After having been an assistant professor of internal medicine at the First Affiliated Hospital of Guangzhou College (China) from 1988 to 1991, he moved to the Albert Einstein College of Medicine (USA) where he has successively worked as a research associate, instructor and assistant professor at the Department of Pathology. Since 2007, he occupies the position of an associate professor in this department. Dr. Huang's studies focus on the molecular disease mechanisms of *Trypanosoma cruzi* and the genetic manipulation of the parasite. He made substantial contributions to the research on Chagasic cardiomyopathy, cAMP-signaling and Mitogen Activated Protein Kinases (MAPKs) in *T. cruzi* and *Toxoplasma gondii*.

2. Interview with Dr. Huan Huang

1. *What triggered your interest in generating an attenuated live vaccine against Trypanosoma cruzi and why did you opt for the inducible suicide system?*

Currently, no suitable vaccine is available for protecting against *T. cruzi* infection, despite considerable research in this area. Although several experimental vaccines provide some protections against *T. cruzi* infection, as compared to live attenuated *T. cruzi* vaccines, these approaches do not provide a strong and long-lasting immunity against *T. cruzi* infection.

In *T. cruzi*, attenuated parasites still pose health risks, since it is has been impossible to eliminate the parasitism in the immunized hosts, and attenuated parasites may revert to virulence particularly when immunized hosts develop immune compromise. To overcome this obstacle, we sought to develop a new method to prevent persistence, based on the introduction

of an inducible detrimental/toxic gene into *T. cruzi*, which results in killing the organism upon the induction of the detrimental/toxic gene. Such an inducible strain could be useful as a vaccine to induce protective immunity. Once a protective immune response is present, any latent parasites could be eliminated by inducing the detrimental/toxic gene, producing a "sterile" immunity. The system we have developed can be used in any strain of *T. cruzi* (including field isolates) allowing this approach to create multiple vaccine strains.

2. *What was your first reaction when you faced the results? Did you expect them?*

We expected the toxin-DDDHA to kill the organism upon induction. However, we also unexpectedly made a discovery when we tested whether the DDD system could be regulated to stabilize fusion proteins in intracellular amastigotes. Human foreskin fibroblasts were infected with pTREX-GFP-DDDHA strain and in absence of induction, amastigotes were replicating inside the host cells normally. Then, 250 nM TMP-lactate was added to the culture medium to induce GFP-DDDHA stabilization, which resulted in intracellular amastigote death. The DDDHA peptide is detrimental to intracellular amastigotes.

3. *How will the project go on?*

This system has significant potential as a bio-safety device in *T. cruzi* which can be used in combination with other techniques such as gene deletion or radiation to develop safe animal and human vaccines.

4. *What is the take-home message of the article?*

We established effective inducible systems for *T. cruzi* employing the degradation domain based on the *Escherichia coli* dihydrofolate reductase (ecDHFR). The DHFR degradation domain (DDD) can be stabilized by trimethoprim-lactate and can be used to express detrimental or toxic proteins to induce intracellular amastigote death. The transgenic strains were attenuated in mouse experiments producing no pathological changes and inoculation with these DDDHA strains in mice provided strong protection against lethal wild type infection. The technique may lead to a breakthrough in *T. cruzi* vaccine design.

5. *Do you have a personal motto, quote or leading sentence?*

"Imagination is more important than knowledge"

6. *What advice would you give to the young next-generation scientists?*

Ask fundamental questions and do good science.

7. *What is your favorite hang-out method after a tough day at the lab?*

Take my dog for a walk.

8. *In your opinion, what are the three most important (scientific) discoveries of the last decade?*
   A. Whole genome projects including human and other species.
   B. Cancer Immunotherapy.
   C. Glaciers Melting Fast.

9. *If you could travel back in time – what historical personality would you like to meet and what scientific discovery to assist to?*

I would like to meet Carlos Chagas in order to define the disease mechanism and invent methods to prevent the disease.

10. *If you could travel forth in time – what eventual invention would you like to check out?*

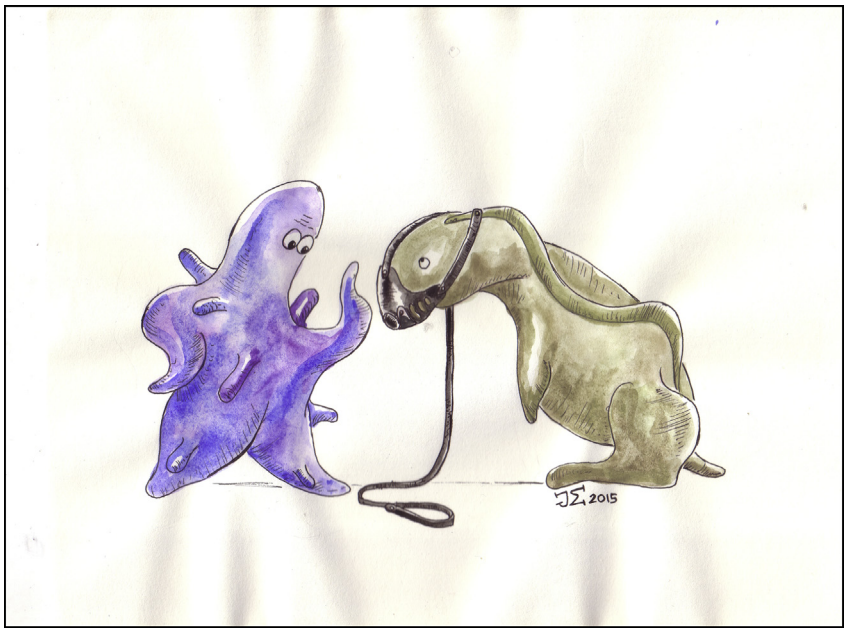
I would like to check out if there will be a safe and reliable vaccine to prevent *T. cruzi* infection and effective and safe drugs for treatment of Chagas disease.

Background

- Vaccines are antigenic substances that provoke an immune response, leading to long-lasting protective immunity against one or several related pathogens
- Vaccines exist against numerous bacterial, viral and parasitic pathogens
- They can consist in inactivated or attenuated micro-organisms, fragments or products of the pathogen as well as chimeric constructs

In a nutshell

- Stable integration of constructs carrying the DHFR degradation domain (DDD) alone or coupled to either GPF, α-toxin or Cecropin A was achieved in *Trypansoma cruzi*
- Sufficient degradation of GFP, α-toxin and Cecropin A by the DDD domain was observed in the absence of stabilization
- Upon addition of trimethoprim (TMP)-lactate, stabilization of the GFP and α-toxin proteins was reached, killing the intracellular amastigotes
- In mice, the transgenic strains are highly attenuated with and without TMP-lactate addition and confer protection against wild-type *T. cruzi*



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