The Three Stooges illustrate why coronavirus-fighting ‘antibody cocktails’ could help contain the virus well before a vaccine

“You imbecile!” bellowed Moe Howard as he stuck a finger up the nose of Curly. Moe the bully would often flick his hand across an unsuspecting face or deliver a two-pronged eye poke to distract from a simultaneous, more serious blow, elsewhere.

Moe, Larry, and Shemp/Curly/Joe were the various incarnations of The Three Stooges, the famed comedy team, with roots in vaudeville, who made films and TV shows from 1922 until 1970. Many of us growing up in the sixties loved them, while many of our parents didn’t. The 2012 film didn’t do the original three idiots justice.

An image of Moe poking Curly popped into my head while reading two new papers in *Science* that report teaming antibodies to tackle SARS-CoV-2, the virus behind COVID-19.

The papers describe the basis of two clinical trials that biotech company Regeneron is conducting to assess a pair of antibodies that work together, binding the viral spike protein where it contacts the human receptor (ACE2) and gains entry into our cells, but at different sites within the “receptor-binding domain.” One antibody is a distractor of sorts, like Moe’s finger-up-the-nose.

The key to the technology is in the coupling. “Our work inventing novel antibodies has shown that individual antibodies, no matter how good, are likely not enough against the devastating virus that causes COVID-19 and the ways it seeks to ‘escape’ being neutralized,” said George D. Yancopoulos, MD, PhD, Co-Founder, President and Chief Scientific Officer at Regeneron.

An antibody cocktail – pitched as “antibody medicine” – provides short-term, passive immunity, as opposed to the lasting active immunity of a vaccine, in which the body learns to manufacture its own antibodies. The Chinese proverb *“Give a man a fish and you feed him for a day. Teach a man to fish and you feed him for a lifetime”* makes the distinction: an antibody cocktail is a fish, a vaccine the ability to fish. Both are needed desperately right now. Antibody protection would last weeks or months.

Viral Resistance is a Natural Consequence of Evolution

The immune system of a host organism, like us, normally produces many different antibodies against a particular infecting pathogen – a “polyclonal” antibody response. Each type of antibody fits into the localized topography of the pathogen’s surface, like keys fitting into different locks.

Not all of the antibodies that an infection elicits destroy, or neutralize, the pathogen. Some antibodies do nothing, while others may actually enhance the infection. But identifying and scaling up neutralizing antibodies isn’t enough, because evolution can get in the way – microevolution, the natural changes in DNA or RNA sequences that happen as these genetic materials replicate. That’s mutation. Then natural selection acts on the new genetic variants that arise by mutation – a nanoscale survival of the fittest.

If a mutation enables a virus to infect and take over a human cell by sneaking into ACE2 by some other route, like a side entrance to a theater, it will soon take over – it has a selective advantage. Teaming antibodies into “cocktails” bypasses evolution by blocking “virus escape mutants” that spread the infection – like Moe distracting Curly or Larry with a hand swipe or eye poke and then walloping him with a clanging frying pan.

Power in Pairs

In one report in *Science*, Regeneron researchers describe how the virus mutates around four types of neutralizing antibodies – when the antibodies are given individually. *Pairs* of antibodies don’t stop the escape mutants if the targets overlap in space, partially-shared nooks and crannies. But when pairs of antibodies dock at physically separate parts of ACE2, escape mutants aren’t seen.

Regeneron has already gotten promising results in a clinical trial of a triple-antibody cocktail (REGN-EB3) to treat Ebola virus disease. And viral escape mutants proved a challenge in developing anti-retroviral drugs against HIV.

The second *Science* paper describes the sources of the antibodies: humanized mice (which have the genes encoding human immune system proteins) and B cells (white blood cells that produce antibodies) from three patients who’d recovered from COVID-19.

The researchers isolated thousands of human antibodies offering varying abilities to bind the receptor on human cells and to neutralize the virus. Then, like a dating app, they looked for good matches.

“We selected pairs of highly-potent individual antibodies that simultaneously bind the receptor-binding domain of the spike protein, providing ideal partners for a therapeutic antibody cocktail that aims to decrease the potential for virus escape mutants that might arise in response to selective pressure from a single antibody treatment,” they write.

Here’s an infographic that shows how the “antibody medicines” work. I’d at first thought that name a bit too dumbed down, but it’s necessary to distinguish the approach from antibody testing as well as from the mixed bag of convalescent plasma.

Regeneron is now conducting two clinical trials of the antibody pair, “REGN10933+REGN10987 combination therapy,” aka the “REGN-COV2 cocktail,” administered in a single intravenous infusion. Both trials are placebo-controlled, accelerate the three clinical trial phases, and assess clinical improvement, adverse effects, allergic reaction, and change in viral shedding in the nose and throat, as well as in saliva.

One trial is enrolling 1,054 ambulatory patients with COVID-19 and expects to have results by the end of November 21, and the other began enrolling 1,860 hospitalized patients this June and expects completion by March 2021. These sicker patients are being considered by the severity of their illness: those on low-flow oxygen, high oxygen, and mechanical ventilation, which should help pinpoint when the antibody cocktail is most helpful.

More Than a Treatment

An antibody cocktail may do much more than help people who are already sick– it also may be used to prevent infection, especially in high-risk environments like prisons and nursing homes when initial cases appear. The strategy may also help people who may not respond well to a vaccine, such as the immunocompromised and the elderly.

Meanwhile, antibody medicines can also provide a bridge until vaccines are available. And researchers can use bioinformatics to induce antibodies against *other* coronaviruses, even ones predicted to be possible to exist based on genome diversity information, which might enable the creation of a stockpile from which to draw when novel viruses emerge in the future. *Precision preparedness.*

Summed up Dr. Yancopoulos, “REGN-COV2 could have a major impact on public health by slowing spread of the virus and providing a needed treatment for those already sick – and could be available much sooner than a vaccine. Ultimately, the world needs multiple solutions for COVID-19, and the innovative biopharma industry is collectively working hard to help as many people as possible with a variety of complementary approaches.”

I mean no disrespect by comparing the dual antibody approach to *The Three Stooges*. I think both are brilliant!

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