W. DAVID FREEMAN: Thank you for the kind introduction, David-- Dr. David Miller, our stroke director. So hopefully this will be a nice casual but light-speed talk, in terms of various veins of research to advance stroke systems of care. And I don't have any financial disclosures. Maybe I should, with relation to some of the technology that we built together, but it's all to benefit the patient.

These are the objectives. The focus of this brief talk is really on intracerebral, or intraparenchymal hemorrhage. I'm going to make the point that a design or engineering mindset is what we need for ICH care. Third, we're going to talk about our Mayo Clinic mesenchymal stem cell research that has taken us about four years, under the leadership of Dr. Abba Zubair, James Meskin, and our Mayo team.

I'm going to touch on minimally invasive neurosurgery for intracerebral hemorrhage. And this will dovetail beautifully in Dr. Kai Chachona's talk in neurosurgery about this, following mine. And then I hope to provide a glimpse of what I think the future of ICH care might look like.

And so this is the nature of the problem. We know that 15% of strokes are hemorrhagic. We don't know until they show up with a CAT scan if they're hemorrhage or ischemic.

I would argue that ICH is an orphaned disease with the NIH, in funding. Yet it's also one that's disproportionately more deadly than ischemic stroke. What's painted in the right upper corner is the elevated intracranial pressure that happens until a ventricular drain is placed. And we have to monitor cerebral perfusion pressure.

We have a paper with Wendy Xia, Dan Hanley, and Johns Hopkins coming out, showing that when CPP is low, patients do worse. So simple placement of an EVD and some other things can help. Also in the bottom right, you can see that there are a number of failed pro-inflammatory mitigating substances-- minocycline, deferoxamine. And we hope to do a study this year on the [INAUDIBLE] stem cells, showing that they reduce damage.

And on the left, we've spent the last 12 years studying what we call CLEAR, looking at catheter-based work, clearing blood out of the ventricles. So what you see in the middle of the screen is the damage that intracerebral hemorrhage causes by leak in the ventricle. And you can see that that black arrow shows the contralateral lobe perfusion from the midline shift.

And this is just another depiction. On the far left is a CAT scan. That white area's the hematoma. And the cartoon is in the middle. And that destroys and displaces white matter tracks.

And this is the nature of the problem. But we know that these patients ride through a neuroinflammatory cascade with neurogenic fever intubated. And we still don't have an FDA-approved drug for intracerebral hemorrhage, despite all these years.

So looking at this quote from 1910, William J Mayo said, "the best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary." So why do I bring that up? This is quite prescient in 1910. This is a century and eight years ago or so.

A union of forces-- as we've evolved technologically, we've all become sub-specialized. But if you look at the way NASA and other teams work together, they get all the team specialists together to put a man on the moon. And that's exactly the stance of the National Academies of Science Engineering and Medicine. And that's the stance I would posit to you that we need to attack for intracerebral hemorrhage.

So I'm going to give you some glimpses of what we've done from a system engineering standpoint, as a medical center, using what we call the SEEPTE-- the safe, effective, efficient, personalized, timely, and equitable approach for ICH. And another way to look at this data is a snapshot in 2018. On the far left, what you see is the prehospital phase. And I'm going to show you some really cool high-tech work that we're doing with the Center for Connected Care.

And I would argue on-- as you can see in the bottom left, because there is no FDA-approved treatment, these patients often languish because there's no obvious surgery or medical treatment. Also the Time is Brain mantra applies to ischemic stroke, but why not intracerebral hemorrhage? For every 1 minute is 1.9 million neurons. And I'm going to show you some data, how we save about 14 million neurons in about 7 and 1/2 minutes, by offloading just a simple component, called the NIH Stroke Scale.

I'm going to touch on the hospital and the ICU phase with some earlier interventions and work we did with some catheters in the clear trial and then touch on mesenchymal stem cells on the third circle there. Because there is no FDA-approved drug-- and this is all to get back to the circle of life, if you will, to prevent stroke. So this is some brand new work. I would mentioned, four years ago, we did a cutting-edge pilot using Apple iPads and Verizon.

We showed feasibility that with LTE signal inside of a moving ambulance, you could obtain an NIH strokes scale. And you could save 7 and 1/2 minutes. And you can see this takes an entire team of collaborators, you can see there. You can see this was from a couple weeks ago. We moved on to our project, now-- used the simulation center to train our neurology residents to do this using a different platform.

And this is basically-- I would argue there's a lot of movement in the stroke community to use what's called a mobile stroke unit. Now mobile stroke unit costs about $1.5 million. This one is simply equipped with telemedicine. So this one, I would argue, is his lower cost and may be more cost effective. And we're working with the Harvard Business School to look at all the indirect things at the Center for Connected Care.

So this is a short movie just to give you a paint through of what's--

[VIDEO PLAYBACK]

[MUSIC PLAYING]

-
[INAUDIBLE]
1, 2, 3, 4, 5,
[INAUDIBLE].

-
[INAUDIBLE].

-
[INAUDIBLE].

- Moderate overflowing [INAUDIBLE].

[MUSIC PLAYING]

[END PLAYBACK]

W. DAVID FREEMAN: So just to give you an idea, the device that we're using is FDA Class II medical device to get the NIH Stroke Scale of the patient before they ever arrive. Some exciting things that we're learning, that we can tailor the patient's therapy by getting eyes on the patient earlier. Do we need to activate on a seizure or not, what destination they want to be or not.

And this is the future, I think. And I should mention, two days ago, they asked me to beam in-- just to shoot some of these videos, and I did it from my iPhone over from the Mangurian building. So to show you that this is feasible and the power of Moore's law.

The other cool thing is-- this is Dr. Chris Keiper examining a patient in route and Dr. Jamali examining a patient in route. So what do we need to be redesigning? I think we all know that ischemic stroke pendulum swing happened in 2015 with these landmark trials, like MR CLEAN, SWIFT PRIME, and so forth. The technology changed and so did the patient care.

We saw number needed to treat of two for LVO in the Hermes and a similar database for large vessel occlusion. We need the same thing-- a door to needle time or a metric to push the care for intracerebral hemorrhage patients. And the Center for Regenerative Medicine, we're working on some mesenchymal stem cell trials. Some of the door to IR time-- that's a metric to get someone to the cath lab for a large vessel occlusion in their middle cerebral artery.

We need a similar one for intracerebral hemorrhage. So hopefully at the end of this session, you'll be using the term, door to OR or door to EVD. And this is based on what data you're going to see. But rather than bore you with a lot of data-driven slides, I wanted to share a couple patient cases. And these go back, actually, to 2006. So this is now quite a long time ago.

When we were in the early phases, before CLEAR was ever started, this was a Navy SEAL, who had undiagnosed hypertension, who collapsed in front of one of our nurse surgeons, Eric [INAUDIBLE], who happened to be on call and put a ventricular drain in his head. He had a hypertensive hemorrhage. You can see right there on the left, basal ganglia.

And his family was very aggressive, and they said we want to do anything. Now I have to tell you, at the time, CLEAR II B wasn't even online. We documented the risk consent of giving intraventricular tPA through a brain catheter. The family had no problem with that. This is a month later, showing you good thrombolysis clearance. He had some thalamic injury. And he later required a VP shunt for hydrocephalus. But this is three years later.

The son on the far left was so impassioned by his father's story and the missed high blood pressure that he created not-for-profit event here at Jack's Beach, called Never Quit. And the guy on the right's the janitor, who just happened to be the guy who injected his head. And this is the event.

If you're in Jacksonville, you see these everywhere. We kind of take it for granted. So about 5,000 people show up every year. The son is doing an event in New Zealand, Australia, and he's done them all over the world in Afghanistan, as well. You can see the save the date here at Jack's Beach next year.

So a little bit about what we've done with catheters. This was Mayo work in collaboration with Dan Hanley. And basically it summarizes this. We had the hypothesis that the holes on the catheter, shown in red-- if those are all in the ventricle, we could deliver better drug delivery to get the clot out faster. And in the orange box, you can see the brain parenchymal.

And this is a coronal cut of a patient that was actually in the CLEAR trial. And on the far right, you can see those fenestrations, or holes, quite clearly. Now this is a right frontal EVD. And so he didn't have as much intraventricular hemorrhage on that frontal horn. But he did have a lot on the other side. But we showed when you can see the holes on the ventricle, and you're doing intraventricular drug delivery work, it's safer-- you get less tracked hemorrhage when all the holes, or most of the holes, or 75% are in the ventricle.

So on panel A, it's faint to see where those holes are. Panel B, we put those white dots to make it stick out. Panel C and D are the same slice cut, but this is in the brain parenchymal. So this is very something-- you don't need advanced machine learning. You toggle between the brain and bone windows. And this is this patient. He, of course, gave us permission to share his story.

This was his CAT scan. However, when he came into our hospital, you can see he had this very large left caudate hemorrhage and a really thick clot in the left lateral ventricle. And this is the problem. The EVD is perfectly placed through the foramen of monro, and the tip is in the third. The problem that we learned is that patients often get what's called a trap ventricle.

We learned that in the course of the trial. And you can see that he has two catheters in now. And that allowed us to irrigate and thrombolyse that clot. And this is a year later. He was basically neurologically normal. You can barely see where the hemorrhage ruptured around the left caudate nucleus.

This is always what it's all about. In the long hours, it was myself who had to inject him at 2:00 AM on the q8 hour regimen for five days straight. So you really bond with family during this. But he returned, he went back to work, and he attended his son's graduation.

So enough about the anecdotes. What about global data? Why is intracerebral hemorrhage a problem? This is from the global burden of disease Lancet paper from 2015, showing that neurological disorders are number one in disability-adjusted life years. And I'm going to show you-- if you take a snapshot of intracerebral hemorrhage, only about 12% of patients have what we call a really good outcome.

The mortality is gradually lessening, but most cite about 35%. And the majority, 53% percent or so, are left with significant disability. And this is a major problem because if you look at the century of research, we have still no single FDA-approved drug for the disease and surgery. So hopefully you'll be on board with some of the stuff we're talking about.

On the bottom of this figure, what you can see is the age on the x-axis. And on the y-axis is disability-adjusted life year. The purple number is cerebral vascular disease. It's huge. This is a global problem. And you can see it's not only disability-adjusted life years, but death. So ICH is a problem with that.

So hopefully we've got the message across why ICH is, essentially, an orphaned disease that needs newer therapeutics. Hopefully also, we'll make the argument that the pendulum is swinging toward minimally-invasive surgery. And this is going to segue beautifully into Dr. Chachona's talk.

On the far right, this older technology from 2005-- open craniotomy and other methods. Now we have some amazing tools in 2018. This tells you all the failed therapeutics in intracerebral hemorrhage. So CLEAR was an intraventricular tPA versus saline irrigation. The FDA made us have a saline irrigation.

Saline irrigation, I would argue, is not really placebo, but there's no way to blind. The data that came out of CLEAR was that the sooner EVD got in, the better the survival. And there's some other good data that is still coming out. And also the patients who benefited the most had the most IVH.

So I wouldn't say that was a negative trial, in and of itself, but compared to saline irrigation. The mortality rate, also, in both arms, was about 10%. To give you an idea, the historical data, when this was all submitted, was about 80% just leaving someone with an EVD alone.

Now on the bottom left, what does the covariate of treating blood pressure aggressively say? So Interact came out, and we pushed people's blood pressure down to 140. And they said it's safe. It may reduce hematoma expansion. Sadly, ATACH-II, its counterpart in the US, was negative. So blood pressure is not, outside of an extravasating vessel, something that we can say truly changes outcomes.

Now on the far right, what about STICH? The original STICH trial almost had 500 patients in each arm, randomized people to medical conservation in the ICU, versus open craniotomy and some other methods. A lot of problems with that, but I think the technology, it's safe to say, was 15 years old.

MISTIE, it was quite cavalier, in the sense that it put an EVD-type catheter into a hematoma and used tPA. Now tPA, this is a drug of its time. It came out '95. But it's probably not the best drug nowadays. In some views, it's considered a neurotoxin.

But the early results of MISTIE II were promising. MISTIE III results are not yet published, at present. But it'd be striking to see that it is not a positive trial. And in the bottom right, Dr. Chachona is going to talk about this more in detail, about the study that's launching here at Mayo, called Enrich, using a minimally invasive surgery.

So I'm not going to spend a lot of time talking about MIS. Dr. Chachona is. But on the far left, this is an Apollo device. Artemis in the middle. And you can see what they see through the little tube or scope, as you can see the hematoma and minimally invasive ways to take out the hematoma. Now NICO and BrainPath has a very slick product as well. And as you can see, the pre-op and post-op results.

Their patented technology is really going through and splaying the white matter tracks apart up to two centimeters without damaging them, which is a great, revolutionary technology that Dr. Chachona will talk about in greater detail. So this is a movie, with the company's permission, for neurologists like myself, who take care of their patients, to visualize what this is about.

So there's an introducer that goes into the lesion-- now this can be a hematoma or tumor-- splaying across the white matter tracks. And then the endoscopic view would be removing the hematoma. Dr. Chachona's going to review that in greater detail. But you can imagine, this didn't exist 15 years ago for patients. It just didn't when STICH was done.

And why am I positive about minimally invasive surgery? I think, for me, when this article, which is a prism analysis-- and if anybody's done one of those painstaking ones, they went through thousands of articles to come up with 14 randomized or controlled trials with minimally invasive surgery. So what I would do is focus your eyes. When you see MIS-- this shows you the methods-- endoscopic or MIS, minimally invasive-- versus the craniotomy groups that they compared and the prospective, or randomized, trial design.

Now this table shows you the location. This is real world hemorrhages, so both lobar and basal ganglia, which is nice. And you can see the number of patients. On the far right, you can see the hematoma volumes. So 50 to 60cc, these are large hematomas. A golf ball is 45cc. A ping pong ball is about 33cc. So these are large hematomas in the brain.

This forest plot shows you that all the data supports minimally invasive surgery, and it reduces mortality. What this slide shows you is that it's not just saving lives-- we can keep anybody alive now with trachs, and pegs, and vents, and these things-- but also shifts toward good recovery. So not just survival, but good recovery.

So that's a whirlwind tour of the prehospital and intrahospital information. I wanted to touch on the work that we're doing with mesenchymal stem cells. I put the cute little axolotl because my daughter made me do that. But there's a whole nature issue about the genome of the axolotl salamander. It even regrow is its own brain. So we'll have to talk with Abba Zubair about that next.

This is a little short movie clip, if you're interested about his work. Now I will tell you, I didn't get up here to tell you that stem cells are all roses. This is from the New England Journal, on the far right, as well as the New York Times, a cautionary tale. Outside of a clinical trial, I wouldn't recommend stem cells.

The last four years we've spent doing MSC research. Dr. Zubair's lab started in vitro models with-- I'm going to show you briefly-- oxygen deprivation neuron. They're neuroprotective and help those cell lines stay alive. A rodent model, and then also we launched the first United States FDA-approved trial. Also in 2017, I would mention, Dr. Zubair and the team was able to get funding to put the MSC on the International Space Station.

The hypothesis was in microgravity, do they go faster? And in talking with him, they do. And this led us to talking to the FDA and a lot of conversations about injecting them directly through the EVD into the brain because they may have even more regenerative ability. So that's the study I'll mention.

So this is an OGD test. I don't want to bore you guys, especially with food, about this stuff. But on the bottom right, you can see that they co-cultured MSC, and neurons survived better. There's something about the MSC. They provide cytokines and other things that keep the cell lines alive. Moving on to the stereotactic rodent model. Because in vitro is one thing, but this was induced ICH model.

Now what I'm going to show you is the-- this, on your left, is the placebo mouse. And I want you to look at his left frontal paw. He's hemiparetic. And now I want you to look at the MSC mouse, who uses both paws to look around. Now they had to get creative to get the mice to move around, dangling food and those kind of things. But you can see he's moving both.

So what about post-mortem? It's one thing to look at functional activity. The black bars represent 0.51 million and 5 million neurons. The bottom line from this slide is that more is not always better. 1 million neurons worked in mitigating the post-mortem hematoma damage. So this led the preclinical work to the FDA approval.

This is the study design. This as a safety tolerability with two year duration. They've only allowed us to treat 12 subjects as a phase 1 study. And I'm going to show you the trial design. So the first group is 0.5 million cells, 1 million, 2 million, and then the last group, group 4, is intrathecally injected.

And we'll-- with a lot of concern-- to do that. But if they do what they do-- intravenous, say, which is often the mystery. How did they work by mitigating cytokines? They may work even better locally administered.

So I'm going to just touch on other advances in the prehospital phase, which is machine learning. We have a lab in collaboration with NOP Logics. But also there's some articles coming out. And there's quite a number of companies, actually, that are fleecing us, doing a lot faster, quicker work on automated ICH detection.

We've seen in our data that there's a half hour lag by the time an ICH patient comes into the emergency department, by the time that a neurosurgeon or somebody is called to activate the systems of care. And why is that? It's because most emergency medicine physicians don't look at the scan or interpret it themselves, primarily. They rely on our radiologists or somebody. There's a delay in getting the call.

So this may help. And our proposal is to pair this with clinical decision support. So in other words, calculate the ICH score and stuff. Now some other cool things on the opposite end of the engineering side are rehab. So this is Professor [INAUDIBLE]. Here at Brooks, he's the CEO of this Japanese corporation looking at microscopic EMG detection of muscle activity to augment CNS signals.

And what he's pointing to is the classical plateau in rehab. This hasn't changed in, probably, 100 years. What they've seen with the HAL device is this secondary curve in rehab. And so this is very promising. It also, I think, got FDA approved here, first, the United States, here in Jacksonville, of all places, in March of this year. So this is promising for the systems of care.

So just summarizing, I believe the future, by 2025, might look like-- your loved one or somebody who has an ICH will have that spot diagnosis and automated decision support. We have newer anticoagulant reversal agents, if that's present, because we know that that helps. Blood pressure, we still don't know.

Minimally invasive surgery, I think you'll see at the end of the evening, the pendulum has completely swung the opposite way. And I hope that we have an IV door to needle cocktail. Hopefully it will be MSC, or some exosome, or something that mitigates the neuroinflammation with this terrible disease.

Obviously, we need to optimize post-operative care on that regard. There's a lot of people that have been involved in this research. And you can see there. And I couldn't do it without them and thank them all.

I did want to touch on one thing, because I'm quite nerdy on this. And we would do host what's called a convergence conference, which is bringing all the specialists together, science and engineering. And Dr. [INAUDIBLE] in the audience is one of our co-directors. So I'll play this.

[VIDEO PLAYBACK]

[MUSIC PLAYING]

[END PLAYBACK]

W. DAVID And see, patients get better from all the teamwork, is what it's all about.

FREEMAN: