THE STAR

Breakthrough raises hope for AIDS vaccine

By **Joseph Hall** Toronto Star
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The long thwarted dream of an AIDS vaccine has been given a major shot in the arm with a new study that has rekindled hope among many experts that they're on track to an effective protection.

After years of fruitless searching, researchers report today in the journal *Science* that they may have finally acquired an Achilles heel for HIV.

"It's certainly the most exciting news in vaccine research in the last decade," says Dr. Kelly MacDonald, director of the University of Toronto's HIV research program.

A chameleon killer, the virus mutates so rapidly that it has vanquished any effort to create an effective vaccine against it for two decades now.

But in the new paper, researchers say they've found a furtive piece of the organism that remains unchanged through more than 75 per cent of HIV mutations – offering a new and promising target for inoculation.

Scientists say they may know within months how fast and well this new HIV target can be employed in a vaccine strategy.

The segment is located on a part of the virus — a spike — that's key to the virus' infectious prowess. And attacking this site with two potent antibodies revealed in the paper can stop the vast majority of HIV in its tracks, researchers say.

"I would say it gives those of us in the field of vaccine a reason to believe...that there's still some reason to go after the old antibody approach," MacDonald says of the study.

MacDonald, who has been front and centre in the global search for AIDS vaccines, did not contribute to the paper. But she says it shows the $100 million spent on HIV antibody research has not been wasted and that it's proven a host of doubters wrong.

"Whoosh. It's fundamentally proved...that this concept works and that this (antibody) avenue and approach is fruitful," MacDonald says.

"This principle that we've been struggling and working towards for 15 years has been the right idea, we haven't been wasting our time, thank God."

Wayne Koff, vice president of research at the International AIDS Vaccine Initiative and study co-author, says the paper could herald a "renaissance" in the maligned and much thwarted field of HIV inoculation.

"This should be the tip of the iceberg, there should be a number of other antibodies identified, in fact there are other antibodies," Koff says.

After several, much-publicized vaccine failures, Koff says "the field has basically struggled in vaccine design," using antibody immunity.

But the pair of previously unknown antibodies revealed in the paper – discovered in the blood of an unidentified African AIDS patient and known as PG9 and PG16 – appear to neutralize

Antibodies, which are created by immune system soldier cells known as B-lymphocytes, are sent out like Pac-Man gobblers into the blood and attack specific, matching regions of an invading virus.

These viral segments, known as antigens, are protein outcroppings on the surface of the spike like structures that attach the organism to its victim cell and allow it to break in.

Antibodies neutralize this break and enter capacity by attaching themselves, like a lock over a key, to their corresponding antigens – basically turning the virus off.

"The spikes makes contact with the target cell and that's what triggers the whole entry process," says Dennis Burton, the senior study author.

"Antibodies bind or attach to those spikes and stop the virus from making contact...and it just gets cleared away and the infection is aborted," says Burton, and immunologist at the Scripps Research Institute in La Jolla, Calif.

A vaccine mimics the viral region where the antigens sit, and train the immune system to recognize and attack the virus in that vital spot when the real thing enters the blood stream.

Unfortunately with HIV, the antigen regions covering the virus' surface can shift shape with stupefying swiftness – so much so that there may be a million different forms of the virus in any given infected patient.

Thus, to find infecting spike segments that are relatively permanent — or "conserved" — across all HIV mutations has been the holy grail of AIDS vaccine research.

That, says Burton, is what his study appears to have done.

"To get (antibodies) that cover three quarters or more (of HIV), That's really very, very promising," Burton says.

The next step is to isolate the area of HIV that these antibodies correspond to, recreate it in a harmless form, and manufacture a vaccine.

That, says Burton, will be no easy task.

"To go from an antibody to a...vaccine candidate that induces that sort of an antibody is not trivial, we're still struggling to do that effectively," he says.

"I would say this is a very hopeful sign, but it's still not the vaccine."

Canadian Institutes of Health Research scientist Ralph Pantophlet says there were already

But, the Simon Fraser University HIV expert says the new antibodies seem to block infections far better than the previous ones in neutralizing the disease.

Still, Pantophlet cautions that the antibodies have only been tested for effectiveness in test tubes and that monkey trials need to be conducted to see if they work to control HIV in live animals.

Any vaccine that may arise from the study would be solely a protective one, Burton says. He says people already infected with the ailment likely have too many variations of the virus for a vaccine to be effective against them all.

Burton would not hazard a guess as to when, if ever, a vaccine might be ready for mass inoculation programs.

Certainly, he says, it will not be within the few months turnaround time it takes to generate vaccines for seasonal flues each year.

But Koff says a few months' study may well produce a clear understanding of the molecular structure of both the antibody and antigens proteins involved in the discovery.

And that, he says, will give vaccine makers a far better idea of when, or if, a viable vaccine could be produced.

Every expert, however, agrees that the pair of anybody sites alone won't be sufficient to produce a completely protective vaccine.

For that, Burton says, several more antibodies will almost certainly be required.

"I don't think one single antibody will cover absolutely every (HIV) virus in the world," he said, adding that three of four similar discoveries would be needed.

But the search method pioneered in the current paper provides a template for such future finds and the best hope yet for acquiring elusive vaccine targets.

That method, dubbed Protocol G, involved a mammoth examination of blood from 1,800 donors, mainly from Africa, looking for the samples that had the best capacity to neutralize HIV.

Once the best donors were found, further blood samples were taken and the number was whittled down to one.

From that donor's blood some 30,000 different B-lymphocytes were cloned and the antibodies they produced were tested against a slew of AIDS viruses.

Indeed, says Koff, the protocol has already produced several new antibodies that may be more potent than the two reported in the study.