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"Barcode" Cell Sensor Microfluidic System: Rapid and Sample-to-Answer Antimicrobial Susceptibility Testing Applicable in Resource-Limited Conditions

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Many rapid antimicrobial susceptibility testing (AST) methods have been proposed to contain clinical antimicrobial resistance (AMR) and preserve the effectiveness of remaining antimicrobials. However, far fewer methods have been proposed to test AMR in resource-limited conditions, such as for frequent safety screenings of water/food/public facilities, urgent surveys of massive samples during a pandemic, or AMR tests in low-income countries. Rapid AST methods realized thus far have a variety of drawbacks when used for such surveys, e.g., high cost and the requirement of expensive instruments such as microscopy. A more reasonable strategy would be to screen samples via onsite testing first, and then send any sample suspected to contain AMR bacteria for advanced testing. Accordingly, a cost-efficient AST is demanded, which can rapidly process a large number of samples without using expensive equipment. To this end, current work demonstrates a novel "barcode" cell sensor based on an adaptive linear filter array as a fully automatic and microscope-free method for counting very small volumes of cells (~1.00 x 10^4 cells without pre-incubation), wherein suspended cells concentrate into microbars with length proportional to the number of cells. We combined this sensor with an on-chip culture approach we had demonstrated for rapid and automated drug exposure and realized a low-cost and resource-independent platform for portable AST, from which results can be obtained simply through a cell phone. This method has a much shorter turnaround time (2-3 hours) than that of standard methods (16-24 hours). Thanks to its microscopy-free analysis, affordability, portability, high throughput, and user-friendliness, our "barcode" AST system has the potential to fulfill the various demands of AST when advanced facilities are not available, making it a promising new tool in the fight against AMR.

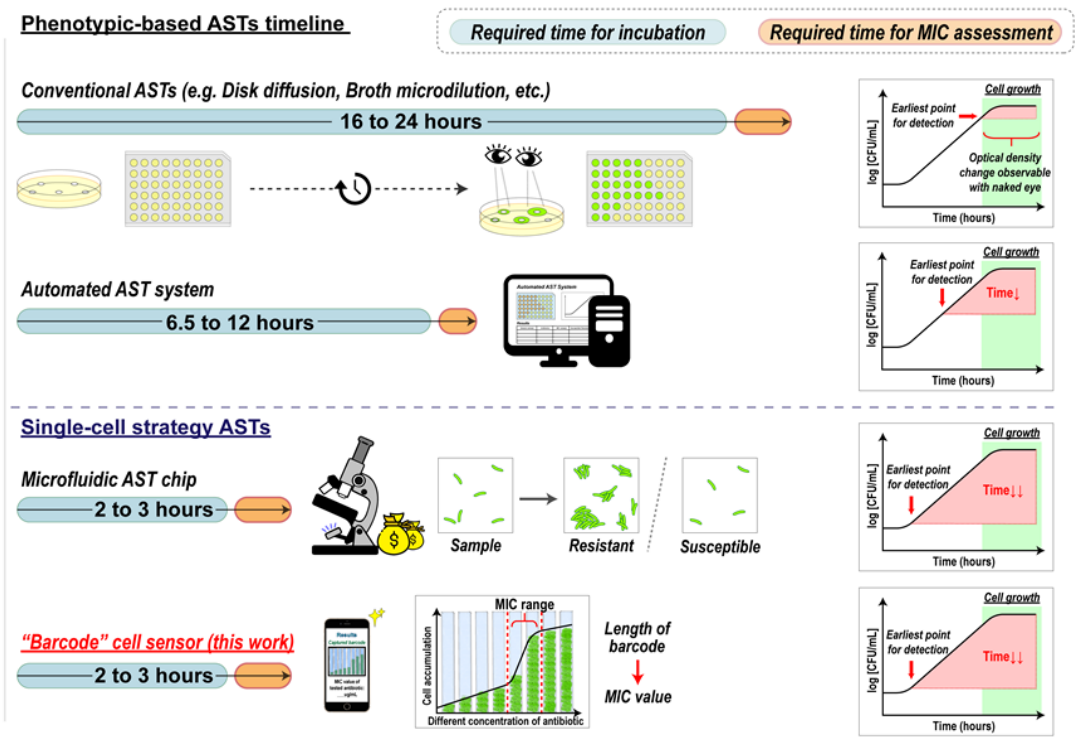

Fig. 1 An illustration of the operation timelines of different phenotypic-based ASTs, including conventional ASTs, automated ASTs, microfluidic-based rapid ASTs, and the AST using a "barcode" cell sensor. The "barcode" cell sensor reported in this work can be coupled with a microfluidic culture device and generate AST results using a cell phone; realizing a practical, portable, low-cost, and high-throughput platform for use in remote and resource-limited areas.

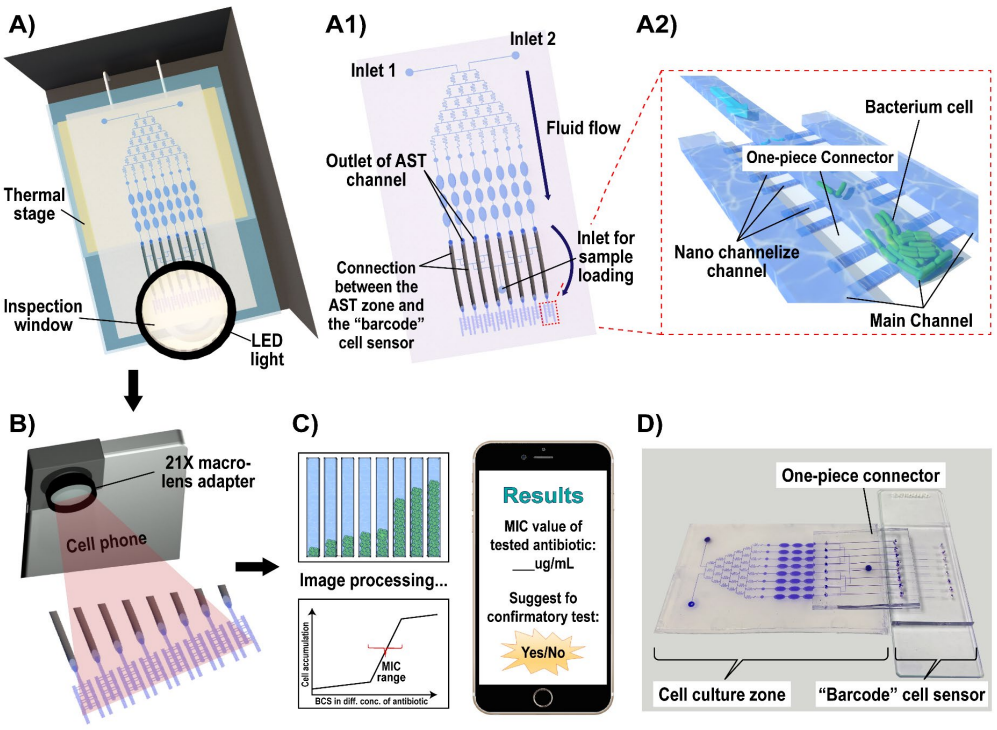

Fig. 2 Design of the portable AST system. (A) The system includes a microfluidic device, an enclosure, a thermal stage, a light source, and an inspection window. (A1) The microfluidic device contains two parts: a cell culture zone (see panel D), which includes a Christmas tree-structured drug concentration gradient generator, followed by micro-chambers with deepened microwells for bacteria culture; and a "barcode" cell sensor. (A2) The zoom-in schematic of the "barcode" cell sensor. (B-C) Bacteria will then accumulate inside the adaptive linear filters in the barcode sensing zone; after Gram staining, the results can be captured and analyzed using a cell phone equipped with a macro lens adapter. (D) The actual picture of the microfluidic device contains a cell culture zone and a "barcode" cell sensor connected by a one-piece connector.

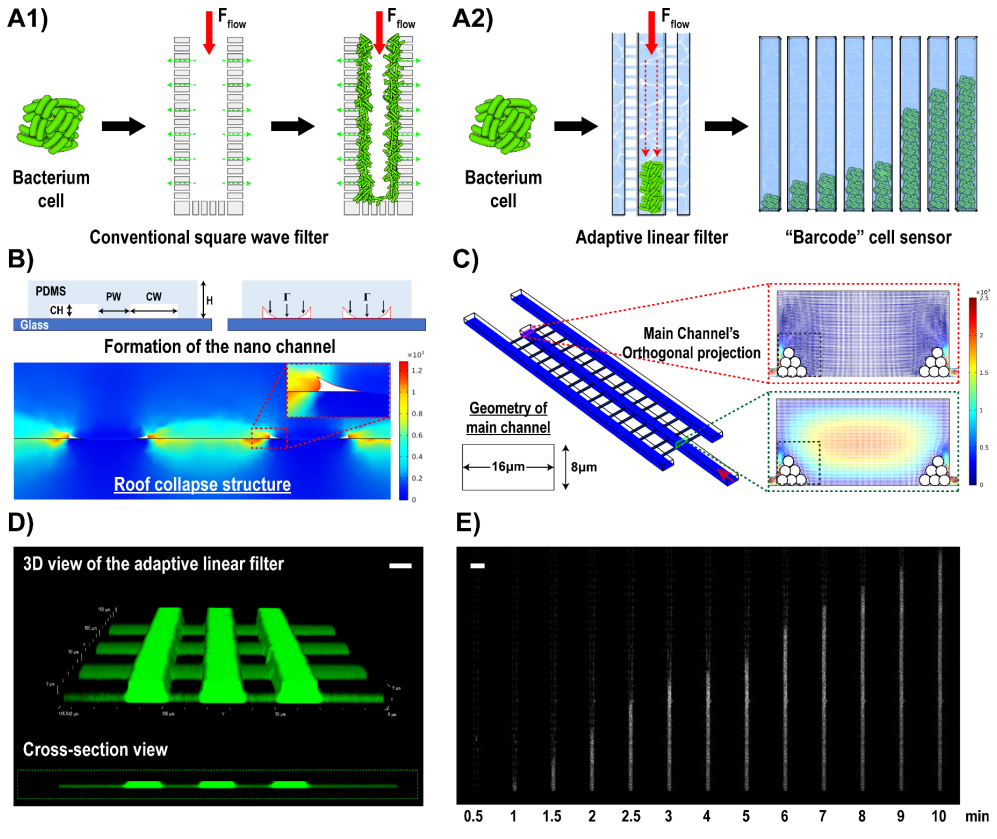

Fig. 3 Schematic illustration, simulation, and testing results of the "barcode" cell sensor. (A) The sensor consists of a group of "adaptive linear filters", each of the filters acts as a "cell number ruler" wherein bacteria injected into the channel will accumulate from the dead-end of it, generating a visible bar with its length proportional to the number of the cells in the suspension. (B) Mechanism of the formation of nanochannels through roof collapse of PDMS channel structures and (C) simulation results of the flow velocity inside the cell sensor. (D) 3D structure of an adaptive linear filter under a confocal. (E) Result of cell accumulation inside "barcode" cell sensor using GFP-labeled *E. coli*.

References

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2. *Han Sun, Chiu-Wing Chan, Yisu Wang, Xiao Yao, Xuan Mu*, Xuedong Lu, Jianhua Zhou, Zongwei Cai, Kangning Ren*, Reliable and reusable whole-polypropylene plastic microfluidic devices for rapid, low-cost antimicrobial susceptibility test,* ***Lab Chip****, 2019.*

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