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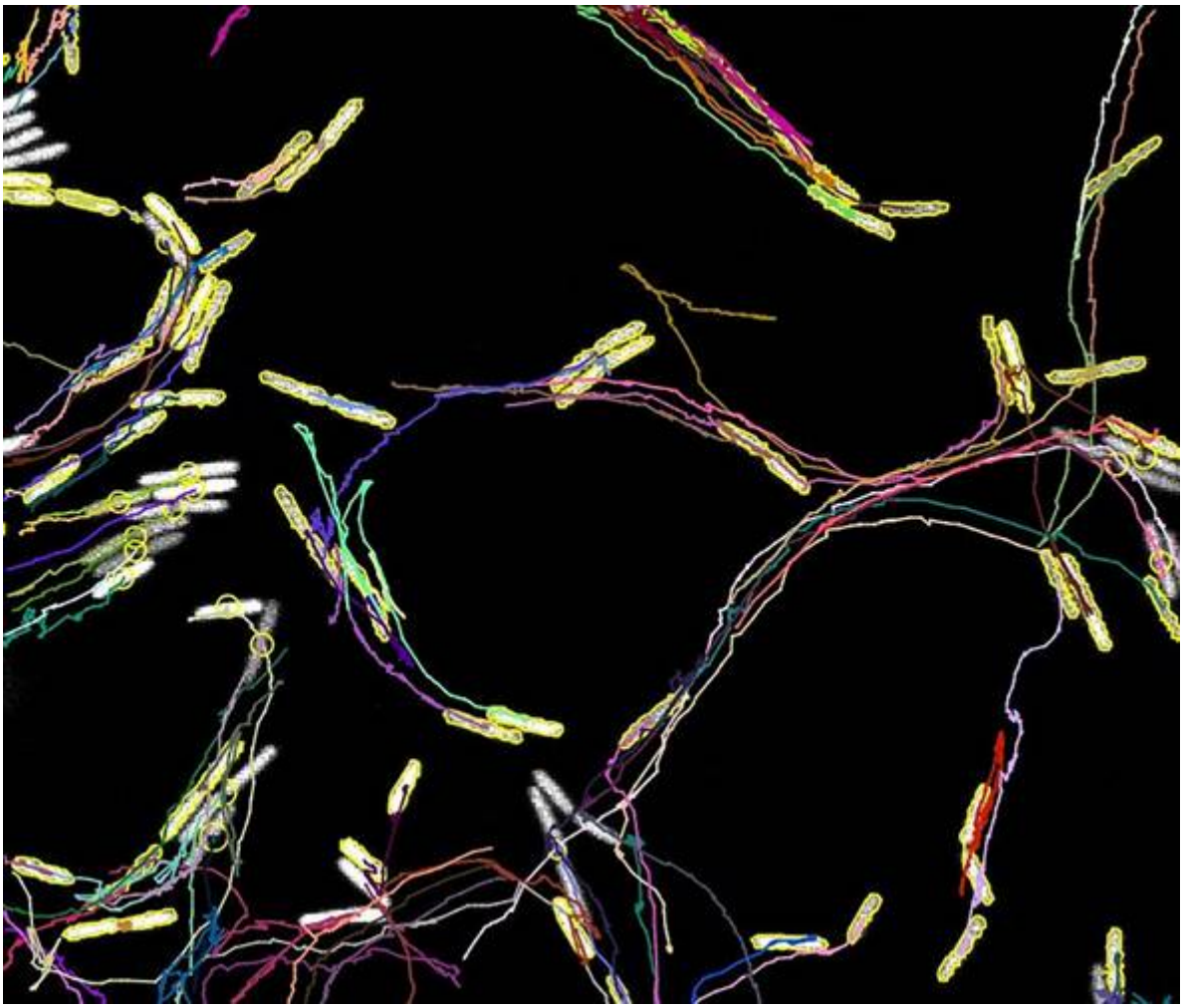

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

IN SILICO ANALYSIS OF BLAZ SIGNAL PEPTIDES FROM *Staphylococcus aureus* CLINICAL ISOLATES: IMPLICATIONS FOR ?-LACTAMASE PROCESSING AND EXTRACELLULAR VESICLE PACKAGING

Robaldi, Stefania [1]- Lopez, Carolina[2] - Bellora, Nicolas [3]- Cassanelli, Pablo [4]- Godoy, Eugenia[1]-Galeano, Mariana [5], Vila, Alejandro[2] -Tribelli, Paula [1,5]

1) Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, UBA, Buenos Aires, Argentina
2) Instituto de Biología Molecular y Celular de Rosario (IBR-CONICET), Rosario, Santa Fe, Argentina
3) Instituto de Tecnologías Nucleares para la salud, Bariloche, Argentina
4) Hospital General de Niños Dr. Pedro Elizalde, Buenos Aires, Argentina
5) IQUIBICEN-CONICET, Buenos Aires, Argentina.
Contacto: stefa.robaldi@gmail.com

Staphylococcus aureus, a pathogenic Gram-positive bacterium, exhibits three primary mechanisms of resistance to ?-lactam antibiotics: enzymatic inactivation via penicillinase (?-lactamase), the presence of mecA gene encoding the penicillin-binding protein 2 (PBP2a) and alteration in PBPs expression. *S. aureus* (SA) cells produce a class A serine ?-lactamase, BlaZ or PC1-1, which is encoded by *blaZ* gene. This enzyme contains a "lipobox" sequence within its signal peptide that anchors the protein to the cytoplasmic membrane of SA. However, a variable percentage of active enzyme has also been observed in culture supernatants, indicating that the enzyme is released into the extracellular medium in a soluble form. Therefore, BlaZ can be processed and adopt two different mature forms. Previous work by the group has shown that membrane anchoring favors the secretion of ?-lactamases into bacterial membrane vesicles (MVs), which can protect the enzyme from extracellular degradation and facilitate its role in cross-protection against antibiotics. To explore this hypothesis in BlaZ enzymes produced by SA from clinically relevant isolates in our country, we aimed to carry out an in-silico study on the signal peptide sequences of the precursor forms of BlaZ, deduced from the *blaZ* gene sequenced from clinical isolates of pediatric patients with cystic fibrosis. The patients were recruited as monoinfected with SA or coinfected with SA and Pseudomonas aeruginosa (PA) and samples were taken every three months or during exacerbations. The whole genome sequence was obtained from 10 isolates of each patient. The in-silico analysis, using the LipoP tool (a lipoprotein predictor), revealed that the 19 sequenced isolates are putative lipoproteins with a high likelihood of being processed by signal peptidase II. All the signal peptides exhibited the same consensus “lipobox” sequence and most of these isolates, 16 out of 19, had higher scores compared to the 3 remaining isolates, two of them corresponding to the same sample, which had scores equivalent to the BlaZ produced by

USA300 used as a reference. The prediction also revealed the second-best prediction, indicating that BlaZ precursors could also be soluble proteins processed by signal peptidase. The 16 isolates that showed higher scores, both for putative lipoproteins and soluble proteins, exhibit 4 amino acid substitutions, in the signal peptide and near the cleavage site, that are likely responsible for the increased efficiency in their processing, which would enhance their chances of being packaged into vesicles. Future research will focus on experimentally validating these predictions in clinical isolates to further elucidate their role in antibiotic resistance and vesicular packaging mechanisms.

Palabras clave: extracellular vesicles-blaZ-antibiotic resistance-S. aureus