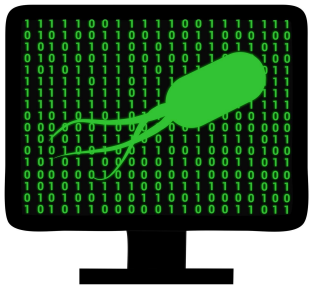

FindTargetsWEB

Identifying Potential Therapeutic Targets on Metabolic Networks of Bacteria

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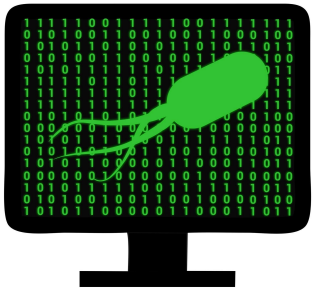
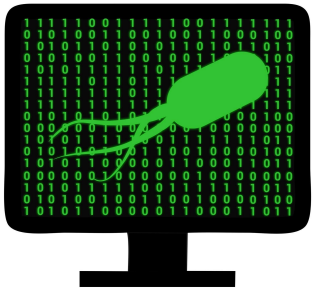
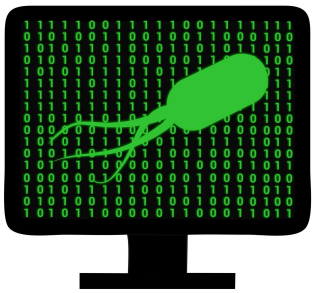


Outline

- **Introduction**
- **Overview of FindtargetsWEB**
- **Algorithm verification**
- **Next Steps**



Introduction



M.Sc. Dissertation

MINISTÉRIO DA SAÚDE
FUNDAÇÃO OSWALDO CRUZ
INSTITUTO OSWALDO CRUZ

Mestrado em Programa de Pós-Graduação em Biologia Computacional e Sistemas

IDENTIFICAÇÃO DE ALVOS TERAPÊUTICOS PARA A BACTÉRIA MULTIRRESISTENTE *P. AERUGINOSA* CCBH4851 ATRAVÉS DA ANÁLISE DE REDES METABÓLICAS

THIAGO CASTANHEIRA MERIGUETI

Paper –Frontiers in Genetics

frontiers in Genetics

TECHNOLOGY AND CODE
published: 04 July 2019
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Check for updates

FindTargetsWEB: A User-Friendly Tool for Identification of Potential Therapeutic Targets in Metabolic Networks of Bacteria

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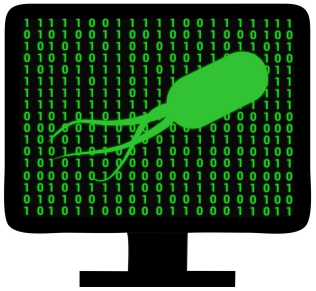
Background: Healthcare-associated infections (HAIs) are a serious public health problem. They can be associated with morbidity and mortality and are responsible for the increase in patient hospitalization. Antimicrobial resistance among pathogens causing HAI has increased at alarming levels. In this paper, a robust method for analyzing genome-scale metabolic networks of bacteria is proposed in order to identify potential therapeutic targets, along with its corresponding web implementation, dubbed FindTargetsWEB. The proposed method assumes that every metabolic network presents fragile genes whose blockade will impair one or more metabolic functions, such as biomass

Identifying Potential Therapeutic Targets

Overview of ***FindTargetsWEB***

Thiago Merigueti



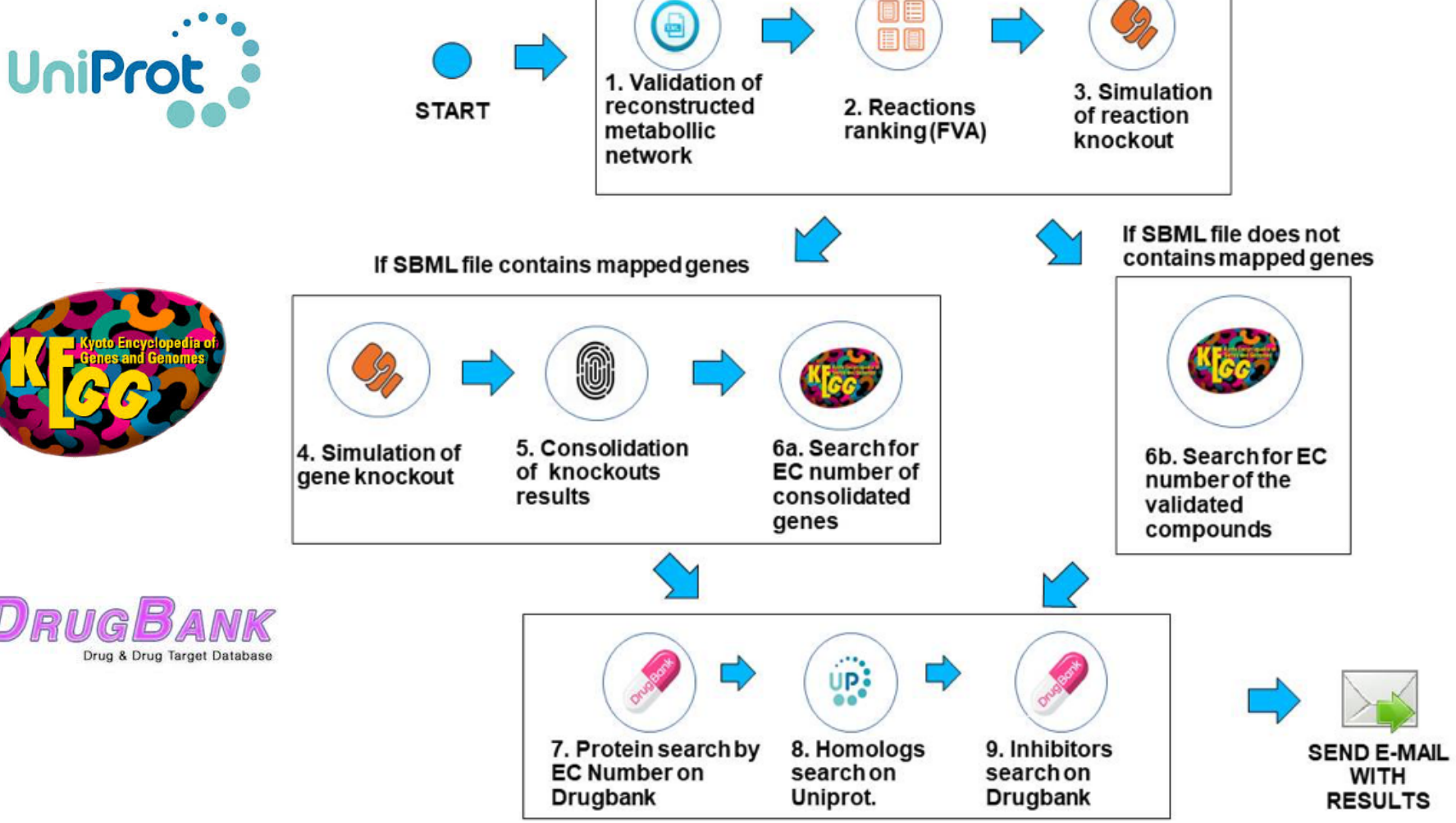
Classification of Metabolic Networks

Tier 1 corresponds to PGDBs that have received at least 1 year of manual curation and are updated continuously.

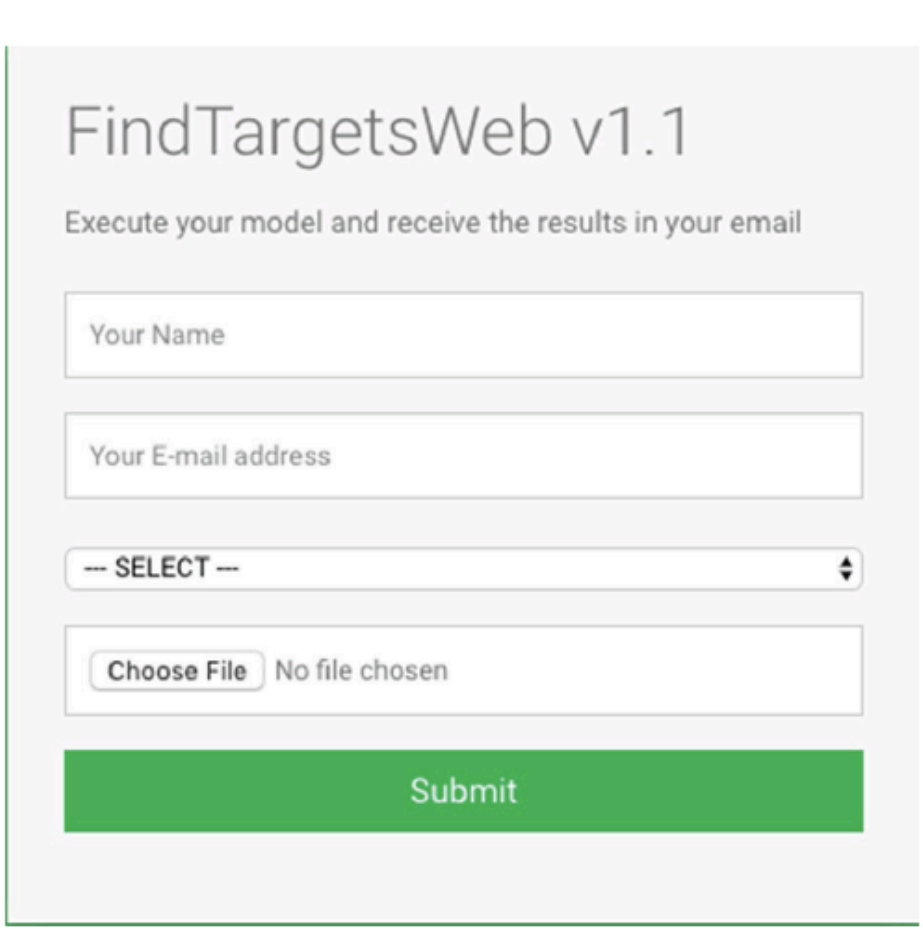
Tier 2 includes PGDBs that have received moderate (less than a year) amounts of review and are usually not updated on an ongoing basis.

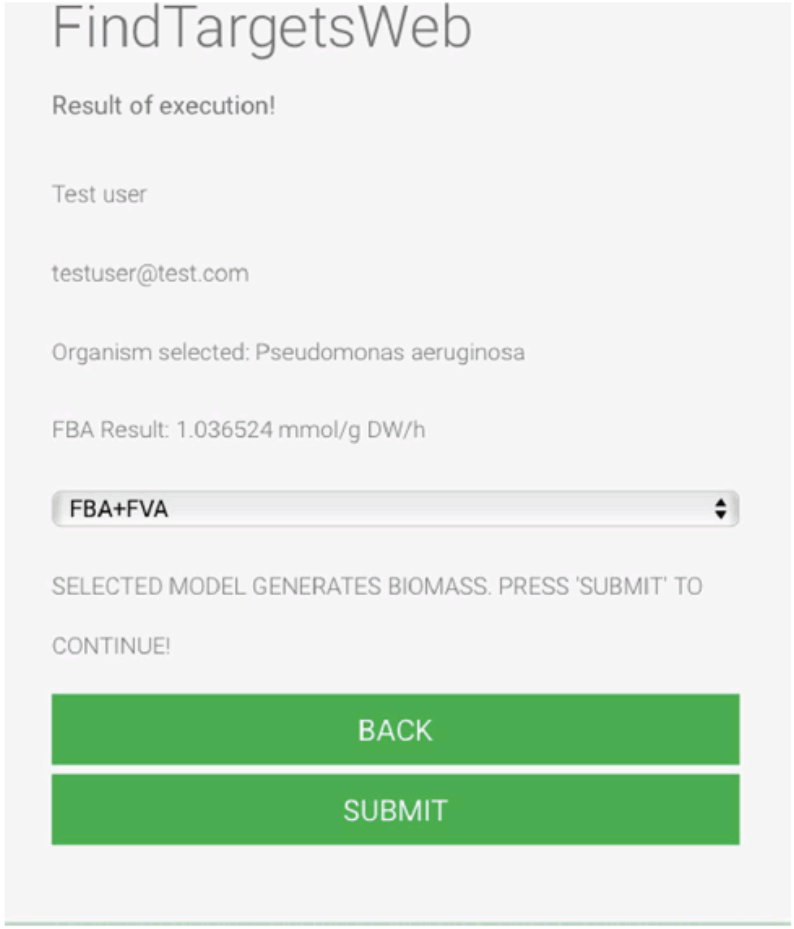
Tier 3 refers to PGDBs that were created computationally and received no subsequent manual review or updating.

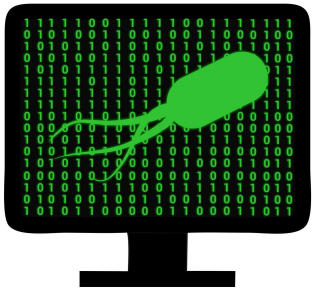
FindTargetsWEB



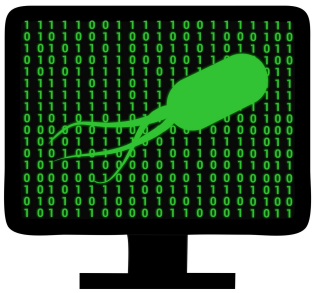
User Interface





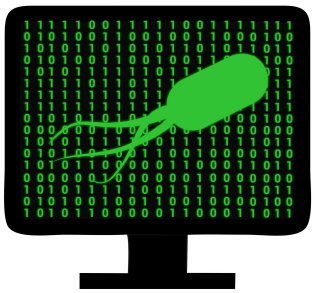


Algorithm Verification



Metabolic Networks

- *Pseudomonas aeruginosa* PAO1 (2008 e 2017)
- *Pseudomonas aeruginosa* PA14
- *Pseudomonas aeruginosa* CCBH4851
- *Klebsiella pneumoniae*
- *Haemophilus influenzae*
- A host-pathogen genome-scale reconstruction based on the *Mycobacterium tuberculosis*
- *Staphylococcus aureus* (gram positive)
- *Pseudomonas putida* (non-pathogenic)

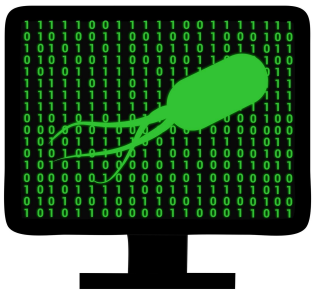


Computational Modeling of Multidrug-resistant Bacteria

P. aeruginosa

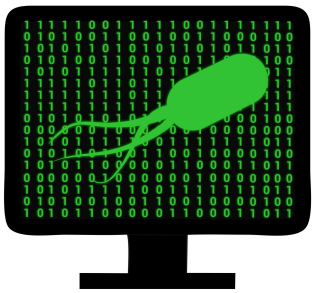
EC Number	Gene Name	Product	DrugBank Inhibitor
1.1.1.100	*fabG*	3-oxoacyl-[acyl-carrier-protein] reductase FabG	E
1.1.1.25	*aroE*	Shikimate dehydrogenase	E
1.17.1.8	*dapB*	4-hydroxy-tetrahydrodipicolinate reductase	E
1.3.1.98	*murB*	UDP-N-acetylenolpyruvoylglucosamine reductase	A/E
1.5.1.3	*folA*	Dihydrofolate reductase	A/E
2.1.1.45	*thyA**	Thymidylate synthase	E
2.3.1.41	*fabB*	3-oxoacyl-[acyl-carrier-protein] synthase 1	A/E
2.4.1.227	murG	UDP-N-acetylglucosamine–N-acetylmuramyl-(pentapeptide) pyrophosphoryl-undecaprenol N-acetylglucosamine transferase	E
2.4.2.14	*purF**	Amidophosphoribosyltransferase	E
2.5.1.15	*folP**	Dihydropteroate synthase	A
2.5.1.6	*metK**	S-adenosylmethionine synthase	E
2.5.1.7	*murA*	UDP-N-acetylglucosamine 1-carboxyvinyltransferase	A/E
2.6.1.16	*glmS*	Glutamine—fructose-6-phosphate aminotransferase [isomerizing]	E
2.6.1.85	*pabB*	Para-aminobenzoate synthase component 1	A
2.7.4.25	*cmk*	Cytidylate kinase	E
2.7.7.23	*glmU**	Bifunctional protein GlmU	E
3.1.3.1	*phoA**	Alkaline phosphatase	E
4.1.3.38	*pabC**	Aminodeoxychorismate lyase	E
4.2.1.24	*hemB**	Delta-aminolevulinic acid dehydratase	A/E
4.2.3.5	*aroC*	Chorismate synthase	A
5.3.1.1	*tpiA*	Triosephosphate isomerase	E
5.3.1.6	*rpiA*	Ribose-5-phosphate isomerase A	A/E
6.3.2.13	*murE**	UDP-N-acetylmuramoyl-L-alanyl-D-glutamate–2,6-diaminopimelate ligase	E
6.3.2.8	*murC**	UDP-N-acetylmuramate–L-alanine ligase	E
6.3.2.9	*murD**	UDP-N-acetylmuramoylalanine–D-glutamate ligase	E

EC number	Gene name	Approved drug
1.3.1.98	*murB**	Flavin adenine dinucleotide**
1.5.1.3	*folA**	Levoleucovorin
1.5.1.3	*folA**	Isoniazid
2.3.1.41	*fabB**	Cerulenin
2.5.1.15	*folP*	Sulfacytine
2.5.1.15	*folP*	Sulfaphenazole
2.5.1.15	*folP*	Sulfamethoxazole
2.5.1.15	*folP*	Sulfanilamide
2.5.1.15	*folP*	Sulfacetamide
2.5.1.15	*folP*	Sulfamethazine
2.5.1.15	*folP*	Sulfamethizole
2.5.1.15	*folP*	Sulfisoxazole
2.5.1.15	*folP*	Sulfamerazine
2.5.1.7	*murA**	Fosfomycin
2.6.1.85	*pabB*	Formic acid**
4.2.1.24	*hemB**	Formic acid**
4.2.3.5	*aroC*	Riboflavin monophosphate**
5.3.1.6	*rpiA**	Citric acid**



Examples of putative targets for CCBH4851

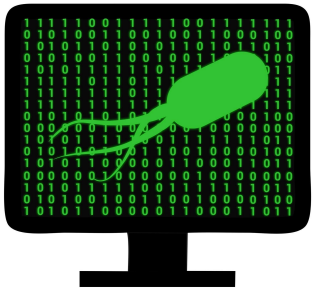
- *algC* - encodes a highly reversible phosphoryltransferase, required for biofilm formation
- *fabA* - participates in fatty acid synthesis (FAS) processes. Attractive targets due to the structural differences between the human and bacterial proteins and the essentiality of FAS



Computational Modeling of Multidrug-resistant Bacteria

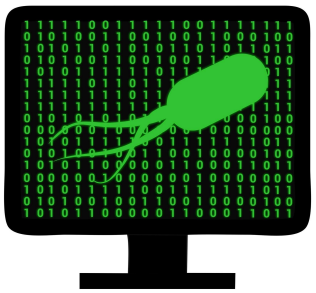
K. pneumoniae and H. influenzae

EC number	Gene name	Product	DrugBank inhibitor	Species
1.3.1.98	*murB*	UDP-N-acetylenolpyruvoylglucosamine reductase	A/E	*K. pneumoniae*
2.3.1.117	*dapD*	2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase	E	*K. pneumoniae*
2.3.1.129	*lpxA*	Acyl-[acyl-carrier-protein]–UDP-N-acetylglucosamine O-acyltransferase	E	*K. pneumoniae*
2.3.1.179	*fabF*	3-oxoacyl-[acyl-carrier-protein] synthase 2	A/E	*K. pneumoniae*
2.3.1.41	*fabB*	3-oxoacyl-[acyl-carrier-protein] synthase 1	A/E	*K. pneumoniae*
2.7.2.8	*argB*	Acetylglutamate kinase	E	*K. pneumoniae*
2.7.4.9	*tmk*	Thymidylate kinase	E	*K. pneumoniae*
4.2.1.59	*fabA*	3-hydroxydecanoyl-[acyl-carrier-protein] dehydratase	E	*K. pneumoniae*
6.3.2.13	*murE*	UDP-N-acetylmuramoyl-L-alanyl-D-glutamate–2,6-diaminopimelate ligase	E	*K. pneumoniae*
6.3.2.8	*murC*	UDP-N-acetylmuramate–L-alanine ligase	E	*K. pneumoniae*
6.3.2.9	*murD*	UDP-N-acetylmuramoylalanine–D-glutamate ligase	E	*K. pneumoniae*
1.5.1.3	*folA*	Dihydrofolate reductase	A/E	*H. influenzae*
2.7.4.9	*tmk*	Thymidylate kinase	E	*H. influenzae*
2.7.7.38	*kdsB*	3-deoxy-manno-octulosonate cytidylyltransferase	E	*H. influenzae*
6.1.1.10	*metG*	Methionine–tRNA ligase	E	*H. influenzae*
6.1.1.2	*trpS*	Tryptophan–tRNA ligase	A/E	*H. influenzae*
6.1.1.21	*hisS*	Histidine–tRNA ligase	E	*H. influenzae*
6.1.1.3	*thrS*	Threonine–tRNA ligase	E	*H. influenzae*
6.3.5.2	*guaA*	GMP synthase [glutamine-hydrolyzing]	A	*H. influenzae*



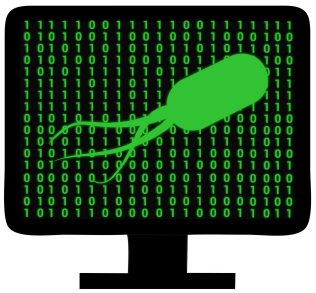
Next Steps

Fabrício A. B. Silva



Algorithm improvements

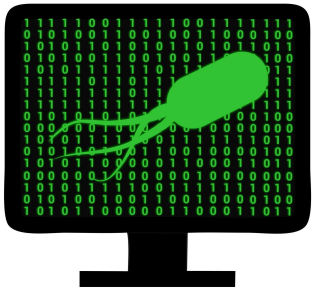
- Identification of choke points
- Define a *priority score*
- Improved topological analysis
- Improved detection of human homologs
- Consider additional data repositories in the workflow



Updating FindTargetsWEB

After the generation of the first integrated model of *P. aeruginosa*, FindTargetsWEB will be updated to search for therapeutic targets on integrated models of bacteria

Subsequent models may require new versions of FindTargetsWEB



Project web site

http://pseudomonas.procc.fiocruz.br

Information about team, software, project status and opportunities

Thank You!

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Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro

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