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► To cite this version:

Philippe Pérot, Béatrice Regnault, Franck Bielle, Jacques Fourgeaud, Éric Troadec, et al.. Necker-Pasteur Clinical Metagenomics: Part 2. Contribution to Pathogen Discovery. 6th International Conference on Clinical Metagenomics, Oct 2021, Geneva, Switzerland. . pasteur-03467165

HAL Id: pasteur-03467165

<https://pasteur.hal.science/pasteur-03467165>

Submitted on 6 Dec 2021

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Necker-Pasteur Clinical Metagenomics: Part 2. Contribution to Pathogen Discovery

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BACKGROUND

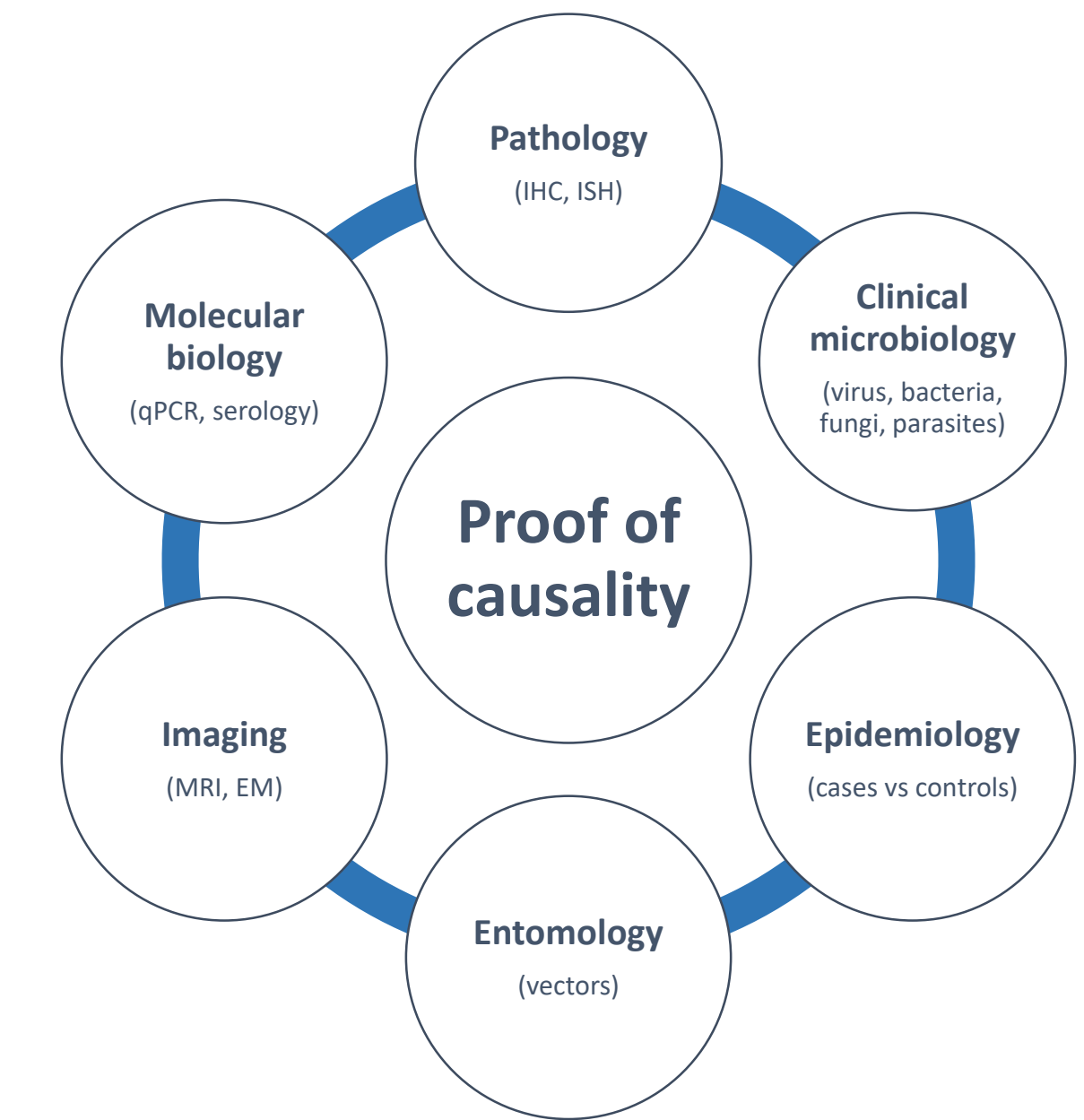
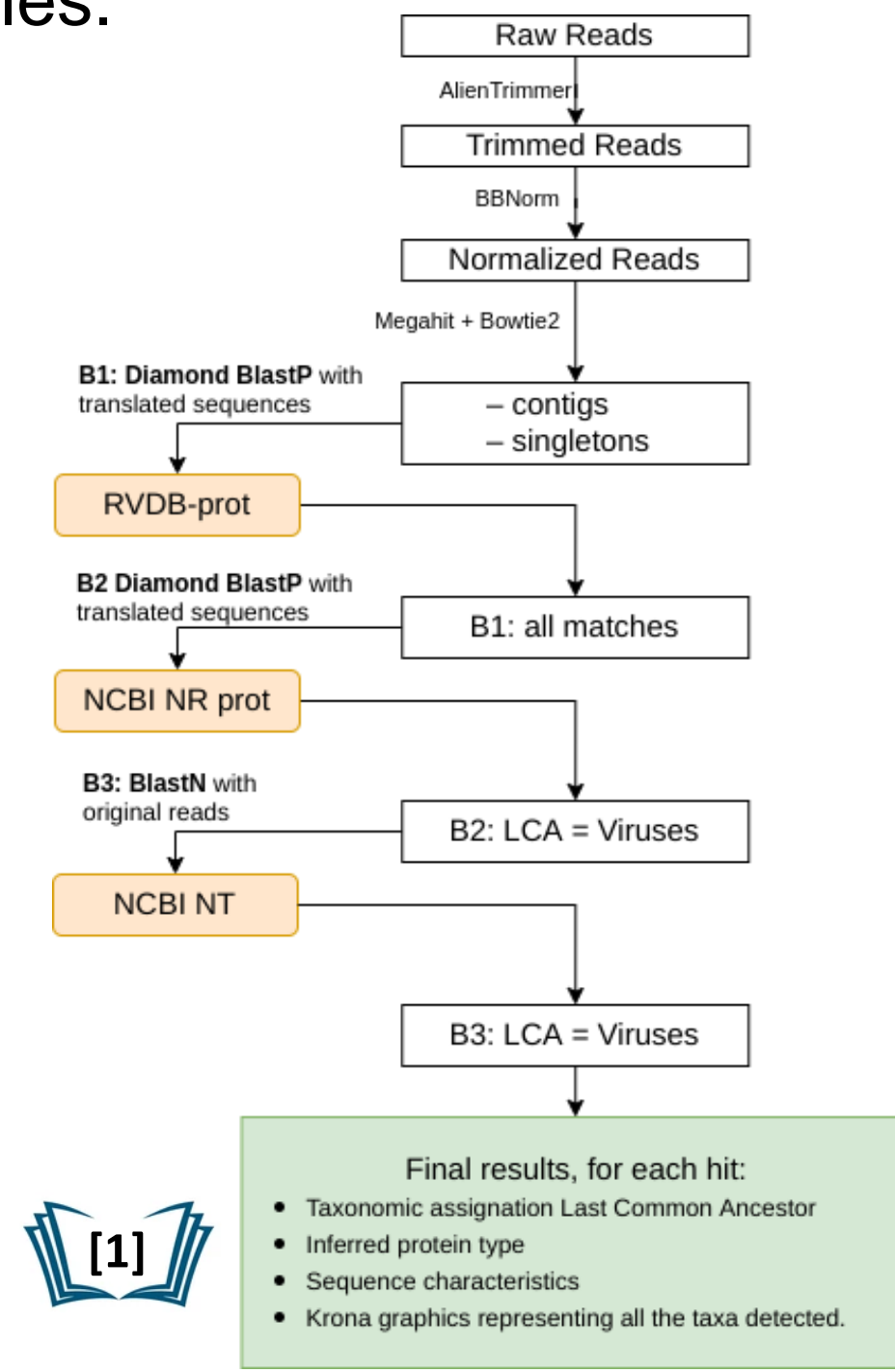
Clinical metagenomics fuels pathogen discovery but a comprehensive research environment is required to address critical questions such as imputability, physiopathology of novel identified infectious agents, and development of new diagnostic tools. The Institut Pasteur, in close collaboration with specialized hospital clinical services and laboratories including (neuro)pathologists, along with other academic labs, seeks to address these topics.

METHODS

We present the research environment, including sequencing and analyzing tools, molecular and cellular biology, virology, histology and entomology resources, that promotes the exploration of novel or unexpected pathogens identified from patient samples.



1. A dedicated sequencing platform, BioIT infrastructure and pipeline



2. A network of trained (neuro)pathologists, virologists, entomologists and molecular biologists

RESULTS

We review some of the major identifications done in the course of our historical partnership with hospitals, by highlighting the place and the contribution of research works following identification of new or unexpected microorganisms. The list includes novel human pathogens with a zoonotic potential (Astrovirus VA1, Umbre orthobunyavirus, European Bat Lyssavirus 1) and known pathogens with unexpected or atypical presentation (Rubella virus, Rabies, Dengue).

Novel human pathogens with a zoonotic potential

Astrovirus VA1

- 14 year old boy, Bruton agammaglobulinemia
- Cognitive impairment noted over the last 4 years
- Ataxia, erratic myoclonus, and dysarthria
- MRI: diffuse cortical-subcortical brain atrophy and periventricular hypersignals
- CSF: normal.
- Histologic findings consistent with acute pan-encephalitis
- Astrovirus VA1 identified by NGS from brain biopsy (in 3 days from sample to result)
- Actionable treatment: ribavirin + pegylated IFN

Umbre orthobunyavirus

- 21 year old man, Bruton agammaglobulinemia.
- No trip outside France.
- Rapid deterioration of the neurological state, tetraparalytic syndrome, progression to mutism and grabatization.
- Post-mortem brain samples: spongiosis (P-P neg), diffuse microglial activation and perivascular inflammatory infiltrates.
- Umbre virus detected by NGS and confirmed by ISH in neurons (f).

European Bat Lyssavirus 1

- 59 year old patient without past medical history.
- No travel outside France in the previous 2 years.
- Bats colony lived in an outbuilding of his house.
- Phono- and photophobia, vomiting, dysarthria, and swallowing disorders, progression to a nonreactive coma and clinical seizures.
- abundant inflammatory perivascular infiltrates, astrocytic gliosis, and microglial activation, limited necrosis. Loss of Purkinje cells.
- Identification of European Bat Lyssavirus 1 by NGS.

Known human pathogens with unexpected presentation

Rubella virus, vaccine strain (cutaneous and visceral granulomas)

- Persistence of rubella live vaccine in cutaneous and visceral granulomas associated with a Primary Immunodeficiency (PID).
- 9 PID pediatric cases described by our group in the period 2013-2019: Ataxia-telangiectasia (x5), RAG1 deficiency (x1), RAG2 deficiency (x1), Activated phosphoinositide 3-kinase δ syndrome (x1) and Undefined combined Immunodeficiency (x1).

Rabies (16 months post bite)

- Czech patient in France for tourism. No notable antecedent, sporty.
- Bitten by a dog during a trip to Bangladesh 16 months ago.
- 5 June 2016: Spontaneous onset of pain in the lower right limb. June 18: febrile context, headache, aphasia, confusion, visual hallucinations and hydrophobia. 13 July 2016: encephalic death.
- Repeated CSF analysis: aseptic lymphocytic meningitis.

Dengue (neurologic form)

- Patient from Togo. No recent trip. HIV+ (in therapeutic rupture)
- Neurological worsening in 15 days: headache, ataxia then coma
- Tetraparalytic syndrome, tetraparesis, pseudo-choreic movements of the 4 limbs
- Normal autoimmune balance and normal tumor markers.

2013

2014

2015

2016

2017

2018

2019

2020

2021

Rubella virus, vaccine strain (cutaneous and visceral granulomas)

[6-8]

Rabies (16 months post bite)

Unpublished work

Dengue (neurologic form)

Unpublished work

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CONCLUSION
 Pathogen discovery includes the identification and characterization of new or unexpected infectious agents and the demonstration of their causality, with the objectives of understanding their biology and fostering the development of novel diagnostic or therapeutic tools. The goal of the Pasteur-Necker initiative in the coming years is to become a national center for clinical metagenomics combining patient care and fundamental research with potential for medical applications, for the benefit of science and patients.

ONLINE CONFERENCE OCTOBER 21–22 2021
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