Malaria antibody test development

Newmarket Laboratories Ltd

Malaria antibody test development

The Problem

Blood transfusion services losing too many donors under long deferral system

Deferral system not 100% effective anyway

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The Task

To develop a test to allow quicker return of deferred donors

To (at least) maintain or (preferably) improve safety of blood supply

Replace laborious IFAT

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The Task

NOT a diagnostic, but an aid to a strategy for maintaining donor numbers

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Development targets
-for users

Compatible with transfusion laboratory strategy and practise

Simple and cost-effective

High sensitivity and specificity

Reactive with all four *Plasmodium* spp infecting humans

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Development targets
-for developer

Make as much use as possible of existing knowledge and reagents (for speed of development)

Commercially viable with respect to costs and IP protection

Microplate format to start

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The problems

Relatively few samples available from known cases

Many samples with questionable storage histories

Many samples with unknown or inadequate case history – particularly with respect to time of exposure/infection relative to that of sample draw

No seroconversion panels available

No true “Gold Standard” test – only comparator IFAT

Only *P falciparum* cultivable

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Some solutions

Collaborations with academic and research institutions - identify highly conserved and immunogenic antigens

Make use of prior work in vaccine research

Merozoite surface proteins (MSPs) showed most initial promise, and recombinants were already available

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Some solutions

“Common” antigens - aldolase, dehydrogenases, not very immunogenic – antibody titres low and variable

MSPs are immunogenic and repeatedly exposed to the immune system, with portions being shed into the circulation.

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Technical Considerations

"Recombinant antigen sandwich" format (recombinants on solid phase AND in conjugate) preferred

Very low backgrounds, high S/N ratios

Very economic use of materials

Good stability, and robust in "guard-band" studies

Undiluted samples can be used – eliminates one diluent, and sample presence in well can be confirmed by OD reading

Detects all Ig classes

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Need for multiple antigens

One recombinant	Sensitivity	69%
Two recombinants	Sensitivity	73%
Three recombinants	Sensitivity	82%
Four recombinants	Sensitivity	99%

Now use 3 *P. falciparum*-derived and one *P. vivax*-derived recombinants

More can be added in when suitable antigens identified

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Performance

Pre-launch

P. falciparum	94.4 %
P. vivax	100.0 %
P. malariae	80.0 %
P. ovale	67.0 %

However, numbers for P malariae and P ovale very small, so results not statistically valid

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Performance

Post- launch		
P. falciparum	106/108 film positive	98.1%(CI 93.5 - 99.5%)
P. vivax	12/12	100.0% (CI 75.7 – 100.0%)

Seed C.R. et al; Vox Sanguinis (2005) Vol 88, pp 98-106

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Performance

Seed C.R. et al; Vox Sanguinis (2005) Vol 88, pp 98-106

These authors calculated that the extra risk imposed by using this test in their operating environment (Australia) was

One infectious P falciparum donation per 175 years

One infectious P. vivax donation per 4.2 years

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Ongoing Development

Improve performance

Ongoing collaborations with researchers, using bioinformatics to help identify more useful antigens for gene sequencing and recombinant construction.

(Several candidates identified)

Possibility also of identifying antigens useful as markers in improved antigen-detection diagnostic

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Ongoing Problems

Still limited numbers of samples, particularly from *P malariae* and *P ovale* infections

More intensive work on genomes of these two rarer species only just beginning

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