Can this man beat the dopers?

Could a new test yield the decisive breakthrough against doping — or does the fight remain unwinnable? *David Bradford* investigates

Now that the dust has settled after the release of the Cycling Independent Reform Commission (CIRC) report, it seems safe to conclude — without creating so much as a ripple of controversy — that cycling still has a doping problem. Speculation rumbles on about the proportion of riders still cheating: is it 90 per cent — the report's much-hyped stat — or is it 20 per cent as mooted by another respondent? Simply: we don't know, but we do know that doping has not been defeated. The question is: can it, will it, ever be? This is not the end for doping, clearly, but is it just possibly the beginning of the end?

Let us not waste time moralising. It stands to reason that a certain proportion of athletes and interested parties in elite sport are willing to cheat if they believe they can get away with it. The rewards for winning are vast, and humans are corruptible; it was ever thus. Nonetheless, the battle to detect and deter the use of illegal performance-enhancing substances, bolstered by improved testing and tougher sanctions, is getting stronger and stronger. Is the fight against doping finally gaining the upper hand and rendering cheating, if not impossible, at least unduly risky for all but the foolhardy?

The introduction of the Athlete Biological Passport (ABP) in 2008 was an important advance. The passport provides a long-term record of an individual's test results which are monitored and compared over time. It has led to the sanctioning of 14 riders and is widely believed to be exerting a significant deterrent effect. However, the ABP has by no means eradicated foul play; last year in the Astana set-up alone five riders failed tests, and the latest high-profile EPO positive was that of Ag2r's Lloyd Mondory, in March.

"The athlete biological passport has improved sensitivity," says Professor Yannis Pitsiladis. "The problem is that, with first-year undergraduate sports physiology [knowledge], an athlete can alter their blood profile."

Pitsiladis explains that reducing an athlete's haematocrit level (volume of red blood cells) — one key marker recorded by the passport — from suspicious to normal is often a simple matter of dilution.

"Infuse some saline or, even easier, drink two litres of water. It's really not difficult."

There is of course a reliable direct test for the presence of EPO, but it is dependent on a urine sample being taken within 36-48 hours of the drug's administration — whereas the performance-boosting effects last for weeks. Pro dopers, often aided by their own medical advisers, work out smart protocols to minimise the risk of detection. Pitsiladis refers me to a 2011 quote from David Howman, the director general of the World Anti-Doping Agency (WADA): "We are catching the dopey dopers, but not the sophisticated ones."

Untraceable

I am sitting with Pitsiladis in his office at the University of Brighton, where he is head of an anti-doping research unit officially endorsed by the International Sports Medicine Federation (FIMS). He has agreed to talk me through a new anti-doping test he is developing which he believes will be virtually impossible to outsmart. First, though, I want him to elucidate on how cheating athletes are evading detection in the biological passport system.

"They are simply taking small doses of the drug [EPO] — micro-dosing," says Pitsiladis: "When a team of scientists tested this practice in the laboratory, not a single athlete was caught. So while the biological passport is an improvement, we need to build on it with a superior test."

The superior test Pitsiladis has in mind is radically different — in terms of its detection method — from what has been tried before. It aims to uncover each drug's genetic 'fingerprint' — the indelible coding the substance activates and in which performance-enhancement is encrypted. While a drug is taking effect, thousands of tiny messenger molecules called mRNA transcribe instructions for making the proteins that bring about meaningful cellular changes — ultimately, in the case of EPO, the production of more red blood cells. By measuring gene activity rather than the volume of red blood cells, this new approach has a clear potential advantage over the ABP: it measures an array of biomarkers that should be practically impossible to manipulate. What's more, it should be able to detect these genetic markers for the entire time during which the drug is exerting its effect.

This study of gene activity is part of a technology known as 'omics', with distinct but related techniques for the analysis of each stage: from transcription (transcriptomics) to the production of proteins (proteinomics) and metabolites (metabolomics). In theory at least, every drug will leave its own distinct, traceable 'fingerprint'.

My limited knowledge of genetics prompts an initial (possibly naive) question: given that each of us is genetically slightly different, how can this test be universal?

"We are not talking about DNA, we're talking about gene expression," clarifies Pitsiladis. "The pattern should be the ▸

Photos: Chris Catchpole, Graham Watson

same in everyone — we're all humans. This is a fundamental principle of biology called the dogma of life."

The biggest challenge for this type of testing lies not in genomic differences between individuals, then, but in the complexity involved in gene expression within all of us. Genes are being switched on and off all the time, in response to myriad different stimuli, be they environmental, dietary, medicinal (e.g. blood transfusions), etc. For Pitsiladis, it is crucial to identify and isolate the genetic fingerprint left by EPO as verifiably distinct from changes that occur 'naturally' as the result of, for example, altitude training.

"We had to look at the confounders, which include exercise and altitude, to see whether they switch on the same genes. We took athletes to altitude to train and took blood samples from them.

"Are any of the altitude genes the same as those for EPO? Yes, but we were able to eliminate the overlaps and isolate the differences. The data is very positive."

Significant expenses

The science may be very promising, but it's also very costly; anti-doping scientists are constantly battling to secure further funding, often to no avail. To understand this predicament more fully, I arrange to speak via Skype to WADA's science director Dr Olivier Rabin. "Probably a few more million [dollars] are needed to validate the omics approach," he explains. "These technologies are expensive; the microchips used are very expensive, and the fact we are working with humans puts contingencies in the research protocols which also bear a cost… This is a very significant amount of money."

Maxim Iglinsky was one of five Astana men to test positive last year

Why isn't Pitsiladis's project receiving the support it needs?

"When it comes to a well-integrated project that is very costly," says Rabin, "we have to say 'OK, we agree that this is excellent science but we have to break it down [distributing funding among different research teams].'"

WADA has already committed approximately $3m to omics research, but its total research budget for 2015 is only $1.8m (from $6.7m in 2006), and this has to be divided between various research projects.

Pitsiladis makes no complaint against WADA but he is palpably frustrated at how his work is being held back by a scarcity of funding streams. Even so, he seems indefatigably determined to find a solution and attract investment.

"I'm saying, don't finance only me, finance all the best scientists in the field, we'll work together and solve this. Work together, that's the strategy. I don't want to work by myself. Let's produce global consortia. This work will help progress medicine, we could work with industry too."

He doesn't have to wait long to have his wish granted, in part at least. Just days after our meeting, Pitsiladis calls from Greece to delightedly tell me that agreement has just been reached among all the major partners working in the field of sports genetics to work together on the Human Athlome Project, with a specific focus on exercise genetics and anti-doping.

Worldwide collaboration

Is a pivotal anti-doping breakthrough just around the corner? Possibly — Pitsiladis is adamant that omics technologies can be a "game-changer" — but it would be imprudent for sport to pin all its hopes on a single silver bullet. Reliable means of detection are only as effective as the weakest link in their implementation. Weeding out dopers requires collaboration between every sporting nation in the world; there cannot exist 'hideouts' where testing is inadequate or non-existent. The new World Anti-Doping Code is significantly strengthened, with new powers to prosecute the facilitators of doping, and an increased, 10-year period during which past doping offences remain liable to prosecution. The cumulative deterrent effect of these changes is potentially very potent.

Pitsiladis in his FIMS-accredited anti-doping lab

Will genetic 'fingerprints' finally outwit cheats?

Developing the new test is costly and requires further funding

"We are catching the dopey dopers, but not the sophisticated ones"

Equally as important as improved detection and deterrence is the need for far-reaching cultural change: a macro-level attitude shift that refuses to tolerate corruption and demands clean, transparent competition. Some elite athletes will always do whatever it takes to win, so it is vital to instil faith that a) their competitors are clean, and therefore b) it is possible to win without breaking the rules. In Pitsiladis's view, this can and must be achieved through accelerating the progress of medicine and sports science — disciplines that he believes have for too long failed to capitalise on technical advances.

"Fundamental sports science today is over 100 years old, so how can we convince athletes to rely exclusively on sports science and medicine? Even at the best labs in the country, they're still doing what was done 100 years ago. Where's the true development?"

Advances in the omics field will make it possible to test an athlete's physiology with far greater precision, Pitsiladis claims, allowing the application of more intelligent, highly personalised training methods and regimes.

"Once you go above lactate threshold, a lot of genes are switching on and off, so imagine [testing] that instead of using only the lactate threshold which is 100 years old — you could observe the genes and really be intelligent in your training. If these approaches are being used to diagnose, treat and cure cancer, then why aren't we using them in sport?"

Sub-2 project

Revolutionising sports science and medicine is, of course, an ambitious proposal requiring serious investment. Pitsiladis's "proof of principle" solution is the Sub-2 project: a bold attempt to attract world-class athletes, expertise and $30m in funding to help achieve the first sub-two-hour marathon. The project's ambition is to discover and implement a multi-disciplinary package of marginal gains: smarter training, technique, technology and nutrition, underpinned by a step change in the physiological testing and all the while closely monitored by independent anti-doping testers. Developing legal means of improving performance is a critical pillar in the fight against doping, argues Pitsiladis, because doing so removes the incentive to cheat.

Scientific progress will no doubt find new, superior ways to outsmart cheats, as well as new ways to optimise performance without doping. However, science-led solutions may also lead to new controversies and challenges. Novel ways to enhance performance, albeit within existing rules, invariably raise doubts and concerns (see panel). Consider the disputes in cycling surrounding therapeutic use exemptions (TUEs), painkillers and out-of-competition cortisone. Anything that enhances performance but which is neither 'natural' nor accessible to everyone inevitably raises questions of fairness and parity.

The question 'how to defeat doping?' is inseparable from a wider discussion about how far we are willing to let scientific advances — driven by commerce — determine who wins and who doesn't. There are no straightforward answers, but it is a debate that must not lose sight of what is at stake — the future of sport itself — nor become mired in history. ■

'No, the fight against doping is unwinnable'

There are of course those who believe that doping cannot be defeated and that the fight against it is futile. The French philosopher Marc Perelman has argued that sport has become reliant on doping to satisfy its obsession with records and ever-improving performances: "[Doping] has become structural in sport as it is now practised. Modern sport today, without doping, could not exist… Without amazing performances or better still a record — preferably, a world record — the spectacle does not exist and public interest declines."

Perelman acknowledges the contradiction that doping is "deplored and condemned" by the sporting world, but this leads him to the dire conclusion that sport may be forced to "absorb" doping by embracing genetic modification, "producing a new species of sporting mutants".

A more positive, less frightening vision for the future of performance-orientated sport is the advancement of sports science (as outlined by Pitsiladis): new ways to optimise performance without breaking the rules. However, some experts believe that this type of advancement invariably produces new risks, i.e. new opportunities for those who are willing to break the rules or exploit grey areas.

These are the unintended consequences envisioned by Professors Paul Dimeo of the University of Stirling in Scotland and Verner Møller of Aarhus University in Denmark: "The cultural shift towards performance science means that anti-doping rules are viewed in purely functional terms. If you are allowed to take 10 of these pills but not 10 of those, then by all means take no less than 10 of these. The spirit of anti-doping is supposed to be about the level playing field, but the spirit of sport is about doing everything possible to gain advantage over opponents."

Lessons of history

Dimeo spoke to *Cycling Weekly* and expanded on his reservations towards current anti-doping endeavours, specifically in relation to new, improved tests.

"In the past, developments in anti-doping perceived as breakthroughs haven't lived up to their promise. If this [omics] test for EPO proves effective, it might be that EPO disappears but that doesn't mean doping is going to stop. Even if all known performance-enhancing substances were detectable new products will be developed and used by athletes. History shows that the supply side innovates to meet demand. The limitations of science as the only answer to this problem need to be recognised."

For Dimeo, anti-doping isn't working and its failure ought to compel a complete rethink in philosophy and approach.

"At the moment, the anti-doping mindset is to increase sanctions and surveillance. It seems to be as though we have only one line of attack, and it's about increasing the power of authorities over athletes while ignoring the inconsistencies in testing between countries."

So, what is the solution?

"I don't have a specific solution, no one does," says Dimeo, "but if you had a system that was more cooperative among athletes, coaches and doctors, using a values-based approach, we might be better able to address the big questions, such as why is it better to have a sporting career based on integrity than one based on doping, and what are the real risks.

"If we were able to narrow the gulf between the policy organisations and the athletes, we might get more engagement and the solutions might come from athletes and coaches. We need more education and information, not just more science, surveillance and punishment."