



Pharmaceutical Industry Project Management Group

Autumn Meeting – 25th November 2009 – AstraZeneca Conference Centre

TRANSLATIONAL MEDICINE - WHERE ARE WE? IMPLICATIONS FOR PROJECT MANAGEMENT

Tom Halliwell (Roche) and Keith Rodgers (Bodiam Consulting)

Executive summary

R&D has to change in the future, in particular to adopt translational medicine as a fundamental way of doing things. In the past, our industry has been dedicated to a 'linear' model of drug development: choosing a disease, identifying a precise, single target, finding a molecule which hopefully will be a 'one size fits all' treatment - which because of the undifferentiated mix of responders/non-responders, produces an average result, showing a tiny improvement over gold standard therapy. As a result, trials to prove efficacy have become ever larger and the efficiency of the whole R&D process as gradually decreased.

Translational medicine offers a real alternative. It means a much more exhaustive, two way exchange of data, from the disease clinic back to the research bench. It means generating much more understanding of the biological basis of diseases, and the different sub-types of a disease that may respond very differently to treatment. For many diseases, one precise target is meaningless - the true cause may be perturbations in multiple - or a 'network' of targets.

Fundamental to this work is the discovery of meaningful and valid biomarkers. *Pharmacodynamic* biomarkers that provide information *after* treatment about effects of drugs on the biology and the clinical outcome. Developed later but designed for eventual use *before* treatment - *diagnostic* biomarkers that classify patients into types, to inform decisions about which drug will be efficacious, and which will not.

The promise of this, and the personalised medicine that it facilitates, is more innovative medicines, with a higher likelihood of success, predicted much earlier in the pipeline. But it will have a marked effect on our organisations, and on project management. We need a step change in the way we assemble wide, multi-source data. The project manager has to get a more flexible, inclusive team to visualise the totality of the story, as well as planning for drug product *and* diagnostics development, with the complexity and regulatory issues it will produce.



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Introduction

Tom Halliwell (Roche) and **Keith Rodgers** (Bodiam Consulting)

Tom and Keith welcomed everybody to AstraZeneca's Alderly Edge conference centre. Translational medicine is a buzz topic at the heart of all pharmaceutical companies' drive to improve the efficiency of the drug development process, and to address growing world demands for personalised healthcare.

The speakers for the day would address the business and technical issues. The delegates' workshop session would address the impact that this would have on organisations and in particular the project management of development.

What is Translational Medicine and what differences in approach to drug development does it bring?

Thomase Senderovitz, VP Global Exploratory Development, UCB

NOTE: Thomas' presentation slides are available also, in the PIPMG Members' Information Centre

Translational Medicine (TM) will be the key to transform the future of R&D. Currently we may as well flip a coin to predict whether a medicine will work or will not! There are many reasons why big Pharma is stuck in this situation. Our reliance on traditional IP - line extensions, me-toos have been driving lack of innovation. We are seduced by 'one size fits all' and as a result spend vast sums in late phase trials to demonstrate tiny improvements over competitors. In the clinic we still find 30-40% of people do not respond to drugs, and millions of ADRs are recorded every year.

TM is a step change from the traditional 'linear' model of drug development. It is a two-way interplay between bench and bedside, translating in-vivo and human tissue data to the human situation - at every stage of the value chain. It is about massively increasing the knowledge available at early stages - i.e. well before Phase 3. We have to get used to focusing discussion on 'meaning for the patient' when we are discussing target selection. Project managers must get the whole team to agree what data they need to see - and this means massive integration of science and technologies. Visualising and exploring implications of complex interplays of data should be routine - just like it is when building aeroplanes! This calls for IT people with the right mindset - who think about integrating data from huge variety of sources; who help scientists with simulation and visualising networks.

Full acceptance of TM also removes the convenient view of one tiny target as a cause, which if treated precisely, removes disease. Diseases are perturbations of biological *networks*. Our job is to understand systems for hitting more than one target - 'Network base Drug discovery' - replacing 'trial and error' therapy algorithms.

The future is of changed definitions. Molecular rather than clinical diagnosis. From treatment of damaged organs to restoration of damaged networks. There are startling new technologies coming on stream: mass consumer-oriented genetic testing, implanted sensors giving real time information about physiological state when under therapy.

Translational Medicine in Practice (Case Study) - Through the Keyhole - an opportunity to get a better grip on human immunity

Dr Richard Kay, Senior Research Physician, AstraZeneca

NOTE: Richard's presentation slides are available also, in the PIPMG Members' Information Centre

Richard set the scene by describing work with Keyhole Limpet Haemocyanin (KLH). This is from a sea-bottom living organism that humans very rarely meet. Thus it's an ideal 'challenge' antigen that can be employed to measure changes in the immune system. Richard also explained the various components of the immune system - and the TM approach that required measuring changes in all of them and how they are interacting - the only way to get an intelligent picture.

Richard presented a technical case study which is set out in detail in the slide set.

In summary he described KLH as a potent (and safe) immunogen for exploring immunomodulation in volunteers and patients. KLH induces easily detectable immunity and can be introduced into long term clinical trials. His team's work introduced a novel method for reliable assays that uses easily producible reagents and removes the need for human sera collection.

The application of Translational medicine in clinical development?

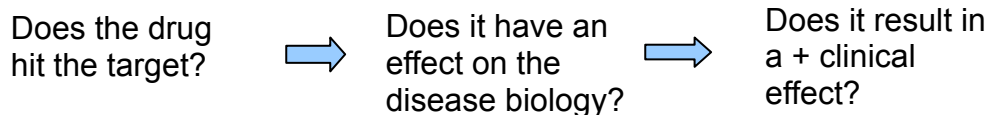
Professor Andrew Hughes, AstraZeneca / Manchester University

NOTE: Andrew's presentation slides are available also, in the PIPMG Members' Information Centre

Andrew set the scene by reviewing the past algorithms for the development of cytotoxic drugs for oncology, featuring 'tumour hunting' with maximum tolerated doses, and large numbers of undifferentiated patients at Phase II. The effect of this is to generate summary results showing small average advantages over current therapy and a requirement for large Phase III studies to prove value. This can result in genuinely valuable molecules being rejected.

Treatment algorithms are enormously complex - what with variation in tumour type, dose, schedule, combinations and patient selection, Andrew calculates '120,000 opportunities to get it wrong!' Today we are far more interested in 'targeted therapies'. Translational Medicine - understanding how drugs work in man - generating plausible and testable scientific hypotheses to address the perennial oncology development questions - around schedule, disease type, combination strategy and so on.

Andrew talked through several real examples, using 'Pharmacodynamic biomarkers': essentially test done *after* therapy, assessing:



These are generally a better guide to effectiveness than 'surrogate' pharmacokinetics. They fix the bottom of the dose-response curve for phase II; they demonstrate evidence of desired effects to support the commercial message.

In summary, personalised healthcare involves testing patients before prescription to enable physicians to identify the right drug, right time, right disease, right patient. To come up with the right drugs in the first place, development means testing trial patients using pharmacodynamic biomarkers. This means a combination for success of: credible target; credible drug; credible biomarker; credible tumour; credible clinical trials.

What is the impact and value of Translational medicine to drug development?

Chris Chamberlain, Biomarker Expert, Roche Products

Chris discussed 'Kitchen sink' translational medicine (!) - in that TM is not a rarified discipline set out on its own, but is integrated as everything you can do to improve the drug development process.

The real value of TM is to attack the all-pervasive statistic of increased R&D spend, and reducing R&D efficiency: it's something to communicate to the shareholders.

TM can help you answer all of the questions about product development, throughout the lifecycle.

Stratified Rx revenue, targeting the responders only, will mean the product revenue will be smaller - this is sometimes good and sometimes bad!

But in summary - we are in the right place for TM.

Appendix: Feedback from Table Exercise

Tables 1 and 5 – Based on what you know and what you've heard today, what do you think are the implications of Translational Medicine for project management and project managers?

(What are the opportunities you see? what are the risks?)

Summary presentation from Table 1:

- We need ongoing, early, two-way awareness. The PM needs a little more knowledge to act as a 'translator' /
- Practical delivery and logistics has to be thought through. 'Silos' need to go.

Summary presentation from Table 5:

- Teams will get broader and more flexible.
- The risk is altered communication flows - with things going back and forward and not progressing. Therefore - empower the PM!

Flipcharts transcription:

Opportunities

Broader, flexible teams - inclusive of stakeholder consultation - to allow data-driven programme management

Risk

Altered communication flows and risk management that needs strong control (PM?)

Building the expertise

...and involving all the stakeholders

Not 'over the wall'

2-way feedback

Training will be key

Flexible team composition

risks

Controlling the feedback loop

Communicating effectively between disciplines discovery / development / technical /

Information platforms

Altered approach to risk management

Tables 2 and 6 – Based on what you know and what you've heard today, what do you think are the implications of Translational Medicine for organizational structure, resourcing (diagnostic/translational medicine expertise) and education/capability development (of team, sub teams, sales force, customers etc)?

Summary presentation from Table 2:

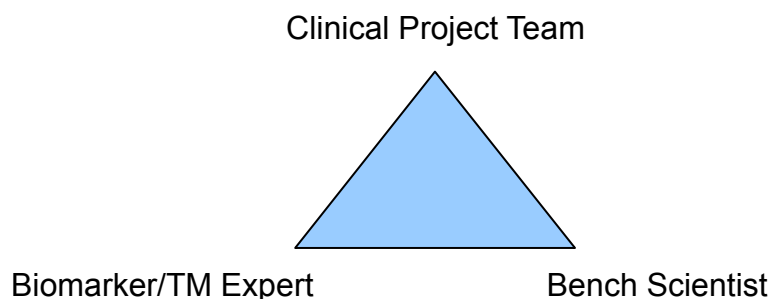
- TM is an art and a science, but all we need is the right people there at the right time
- We must get rid of silos and engage in knowledge sharing - we must understand what each individual can bring to the table

Summary presentation from Table 6:

- We need to enlist external expertise, but ensure an internal knowledge base to be able to manage them
- TM will touch various points on the lifecycle (e.g. 18 months to qualify a biomarker - needs to be built in)

Flipcharts transcription:

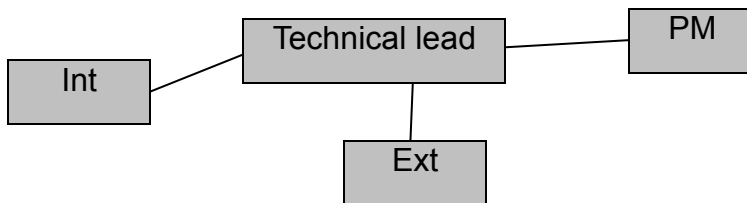
Organisation



1. Expert group (special expertise - e.g. biomarker)
2. Barrier to information (data)
 1. No single point of information
 2. Collection and sharing of data
3. Discovery vs. development
 1. Bringing Research and TM closer together
4. Integrated project management group
 1. Reduce handoffs
5. Discrete biomarker group
 1. de risk
 2. (AZ)
 3. Education
 4. Marketing

6. Therapy area dependent
 1. PV, Safety

External expertise - to bridge gaps and provide latest data
 Internal management
 PM (key: knowledge)
 Technical lead - strategy set up
 Technical internal experts
 Different sized companies - challenge of knowledge transfer



Scientific Advisory Boards for larger companies...?

Education

Cross functional knowledge sharing

- Effective communication
- Light team members
- Communication plan
- Design of trials to exploit biomarkers
- Discrete department
- Self development
- Cross function knowledge sharing
- Ethical aspects considered
- Consent (broad)
- New technologies training
- Team training (e.g. collection of samples)
- PHC (later phase)
- Resource - biomarker experts
- Regulatory aspects
- Priority/exposure of importance of biomarker collection
- Roles and responsibilities
- Pre-clinical staff - biomarker training
- Tell a story!
- Regular attendance at key conferences
- Continuous medical and non-clinical education
- Training budget - invest
- Competence for all - but level varies
- Where to pick up TM in the development timeline?
- Upstream impact on lead times and resources

Tables 3 and 7 – Based on what you know and what you've heard today, what do you think are the implications of Translational Medicine for project scheduling, timelines and budgets (diagnostic development activities and timelines, sample collection etc)?

Summary presentation from Table 3:

- Increased levels of uncertainty as well as the opportunity. PM game needs to be 'upped'.
- Sometimes PM is seen as constraining but the big human factor selling the value of PM.
- A lot more scenario planning. PM linear processes need to be re-engineered. More processes need to run in parallel.

Summary presentation from Table 7:

- Opportunity to de-risk at earlier stages, and identify new applications, market opportunities.
- We need to get in early with biomarker work.
- We need to engage with all members of the project - carry on asking questions - we must have flexibility.

Flipcharts transcription:

- Risk elimination and opportunity hunting
 - Identify questions early
 - Engage Research / Clinical / Commercial
 - Carry on asking questions and evaluating data
 - Flexibility
- Cost, scheduling, timeline impacts
- Change in mind set - invest early / ensure joined-up discussions with right folk - unsure of outcome and eventual return
- Improve attrition rate

Early, ongoing, 2-way knowledge awareness and translation. Practical data-driven application

Tables 4 and 8 – Based on what you know and what you've heard today, what do you think are the implications of Translational Medicine for regulatory (diagnostic test in label etc). what is the expected impact of Translational Medicine on product value in terms of gaining approval?

Summary presentation from Table 4:

- Potential to complicate regulatory dialogue - 'device and product'
- lack of experience in the regulators, of this approach.
- Potential faster, smaller, less risky programmes, based on robust data.
- Issues around whether the payors are warming to all this.
- do we make a point of care diagnostic? Testing must be within clinical trials and these must be approved.

Summary presentation from Table 4:

- An assumption that we will be partnering to develop diagnostics
- There are different outcomes based on whether our drug works, and whether our diagnostic works - e.g. we could envisage development of an expensive, worthless diagnostic if the drug fails.
- Different regulators for each part
- If we are going to have smaller trials, will we still need a large safety data set?

Flipcharts transcription:

Positive impacts

- Potential smaller, faster, less risky programme
- Stronger risk/benefit argument
- Clear patient solution
- Price upside

Negative impacts

- Potential to complicate regulatory dialogue
 - Device (kit) and product
 - Demonstration of device robustness
 - Lack of regulator experience / advice

Registration studies need to be positive for:

- Efficacy of drug
- Δ (effectiveness of diagnostic)

	Drug+	Drug -
$\Delta +$		x

	<p>✓ Selected population</p>	
Δ -	<p>x ?</p>	<p>x</p>

Different regulators
 Multiple consults/iterations with Δ partner.