Future-proofing old school pharma with new biology

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It seems just about every week one of the major news and analysis publications such as *The Economist*, *The New York Times*, *FORBES*, *TIME* or some other major publication drills into the hot-button issue of the perceived disparity between oncology drug pricing and medical-economic value. It is a situation that is undeniably acute considering the following:

1 Many newly approved oncology drugs are costing payers and patients in the range of $100-200,000 for a single course of intervention.
2 For some patients with limited insurance policies, these pricy medicines can be utterly out of reach.
3 For others who do manage to get access, it can mean personal or family bankruptcy (AKA 'financial toxicity'), according to some recent studies.
4 Oncology drugs constitute the second largest category of drugs sold in the US.

So, on top of the economic predicament the current return-on-investment argument the bio/pharma industry uses to prop oncology drug pricing has created a critical medical ethics dilemma.

It is small wonder that oncologists are in rebellion and aligning their collective voice with major payers even as we write this article. The ~35,000 members American Society of Clinical Oncology (ASCO) just released a conceptual framework with the intention to help doctors and patients assess their treatment options based on objective measures of the value of new cancer therapies along three major medical benefits, drug-related toxicity trade-offs, and the cost of the drug plus ascertained supportive care. (http://jco.ascopubs.org/content/early/2015/06/23/JCO.2015.61.6706).

Whatever one makes of the proposed 'ASCO Value Framework', it is a clear signal that a very influential organisation, such as ASCO, is now willing to make a major shift from a vision of drug value anchored predominantly on drug efficacy to a calculation scheme that measures drug cost-effectiveness.

Despite ASCO's gestures with its proposed framework, it is notable that the US is lagging behind several budget mindful European countries that have already adopted oncology drug pricing schemes that are based on methodical calculations of overall cost-effectiveness to the payer system.

Getting crushed from three sides

As influential oncologists seemingly ally with powerful payers and politically savvy patient advocacy groups about a need for better cost-effectiveness, it is not inconceivable that we will see more industry under-performers fade away, or be acquired for residual value.

Simply stated, gone are the days of registering and successfully marketing a cancer drug that provides an incremental survival benefit of a few weeks and that comes with a high toxicity burden to patients.

To minimise the risk of being crumpled under the mounting pressure of value-based medicine from three sides – proscribers, payers and patient advocacy groups – we propose:

1 Future-proofing their business by swift adoption (including partnering) of the most compelling 'new biology' with potential to create a force-multiplier effect (highlighted in the next section).
2 Building into molecules value-based attributes as early as their pre-clinical lead declaration package.
3 Finding ways to establish a compelling economic value story, in addition to demonstrating the standard safety and efficacy profile, at key points during clinical development.

Future-proofing by rationale drug pricing and investing in the new biology

Despite the despondency of drug pricing/value expressed above, it is clear that bio/pharma is back in the limelight of investors. But at the same time, industry

insiders and watchers are concerned the recent trend is not sustainable – memories of the last bull market around the '-omics hype' of 2000 come to one's mind.

As we know, that 'bio' stock sector run-up ended in a spectacular collapse in early March 2000 wiping out billions in aggregate corporate value followed by roughly 13 years of bio-sector under-performance. The bio/pharma R&D productivity crisis coincided with this period and no doubt carried a compounding effect in terms of investor's lowered expectations and trust.

It would seem we have reached a new era where mounting pressure leaves little room for markets to appreciate new medicines from bio/pharma that deliver merely incremental advances in patient care.

To offset the new cost-effectiveness equations, bio/pharma will need to deliver medicines with truly remarkable clinical benefit:risk profiles while displaying far less boldness that has included 'artificial' pricing constructs.

In our mind, the future belongs to those few pharma and biotechs that can exploit 'new biology' the best and the fastest.

'New biology' is applied biology that often occurs at the convergence of orthogonal fields. Two examples of the 'New Biology' would be (1) when a biology challenge converges with engineering, a traditional solution-seeking discipline, or (2) when cancer biologists pay attention to what immunologists studying mechanisms of autoimmunity, inflammation and other T-cell biology inform them.

But what makes the 'new biology' different from the hype of the -omics era that precipitated the crash of 2000?

The key difference is that 'new biology' is actually delivering differentiated products that are truly addressing real unmet medical needs, or pragmatically addressing

New biology: Delivering breakthroughs today and possible future states of the industry

The New Biology	Why it is important	What's next?
Immuno-oncology (IO, iONC) through checkpoint modulation and designer T-cells as drugs	Super-charging cancer patient's 'own' immune system, particularly subsets of T-cells is extending survival for a subset of patients battling aggressive cancers	Understanding which patients will likely respond to checkpoint modulation approaches and improving systemic toxicities (eg cytokine release syndrome, autoimmunity) through biomarkers and next-generation biologic formats. Moving designer T-cells beyond proof of principle. Bridling high manufacturing costs and reducing supply chain complexity to routine practice. Neoantigens/neoepitopes: Evidence accumulating indicates that T-cells unshackled by checkpoint therapy appear to attack neoantigens unique to a patient's tumour. Harnessing TCR (T-cell receptors) recognising these neoantigens is the next wave of IO.
Next-generation sequencing (NGS)	Driving progress to truly personalised medicine.	Migrating from a research tool to on-site patient care applications at hospitals and cancer centres. Key new biology players: Illumina
Gene editing (Genomic Engineering)	Further evolution of designer T-cells to specifically gain, or lose, desired properties that includes; suppressing TCR (T-cell receptors) to improve safety, knocking-out checkpoint pathways to rev-up the T-cells, or engineering resistance to co-administered immunosuppressive therapies	Continual improvement of gene targeting specificity and establishing both clinical and manufacturing proof-of-principal. Key new biology players: Cellectis Intrexon
Intersection of 'Real World' Big Data with Precision Early Molecular Diagnosis/Treatment Decisions	Fighting cancer with intelligently organised and actionable data that provides oncologists with simplified and interactive web-based platforms to help find the best drug match (best hope) for their patients while sparing many patients undue toxicity. Collectively the technologies have the potential to save millions of lives	Continual improvements in precision, 'self-improving' algorithms, while democratising access to cancer genomics datasets in clouds. Key new biology players: Foundation Medicine Flatiron Health Seven Bridges Genomics DNAnexus Genomic Health Theranos
Deep-learning technology ('machine learning') applied to radiology clinics	Potential to enhance the accuracy rate and speed of radiologists and pathologists. Improvement in measuring responses during clinical trials	Linking image analysis to patient outcomes. Key new biology players: Stanford University's 'Computational Pathologist' Enlitic Microsoft's 'InnerEye'

certain shortcomings in the healthcare delivery system.

Despite the major set-back of the 2000s, the bio/pharma industry roared back to life. The rebirth of the bio/pharma industry was made in large part by the blending of orthogonal fields of expertise – so called 'new biology'.

Of course, we anticipate big winners and major losers given the fierce competition and differing rates at which some companies are already embracing new biology and selectively placing their bets.

For example, some bio/pharma companies are 'all in' in CAR-Ts despite evidence that the manufacture-ability could prove quite challenging to margins, while other oncology powerhouses have opted out of the CAR-T races.

Also, it is no secret that many pharma are finally coming to comprehend that their very global reach and scale, which provides them advantages in manufacturing and commercialisation, is the very enemy of creating an innovative discovery culture at the forefront of medical science. We expect those pharmas with the most sophisticated and fluidly adaptive externalisation models willing to partner innovation from those clever few biotechs with a spirit of can-do, to be the ones to flourish in the era of 'new biology'.

No matter the pharma losers and winners, in the best spirit of Joseph Schumpeter's 'creative destruction' premise, it is patients and the healthcare systems who stand to gain the most from these real advances in addressing unmet need through 'new biology'.

In summary, now is the most exciting time in decades to be part of the bio/pharma industry. DDWi