Next Generation Biologics for Cancer Therapy: Beyond the Success of Conventional Monoclonal Antibodies

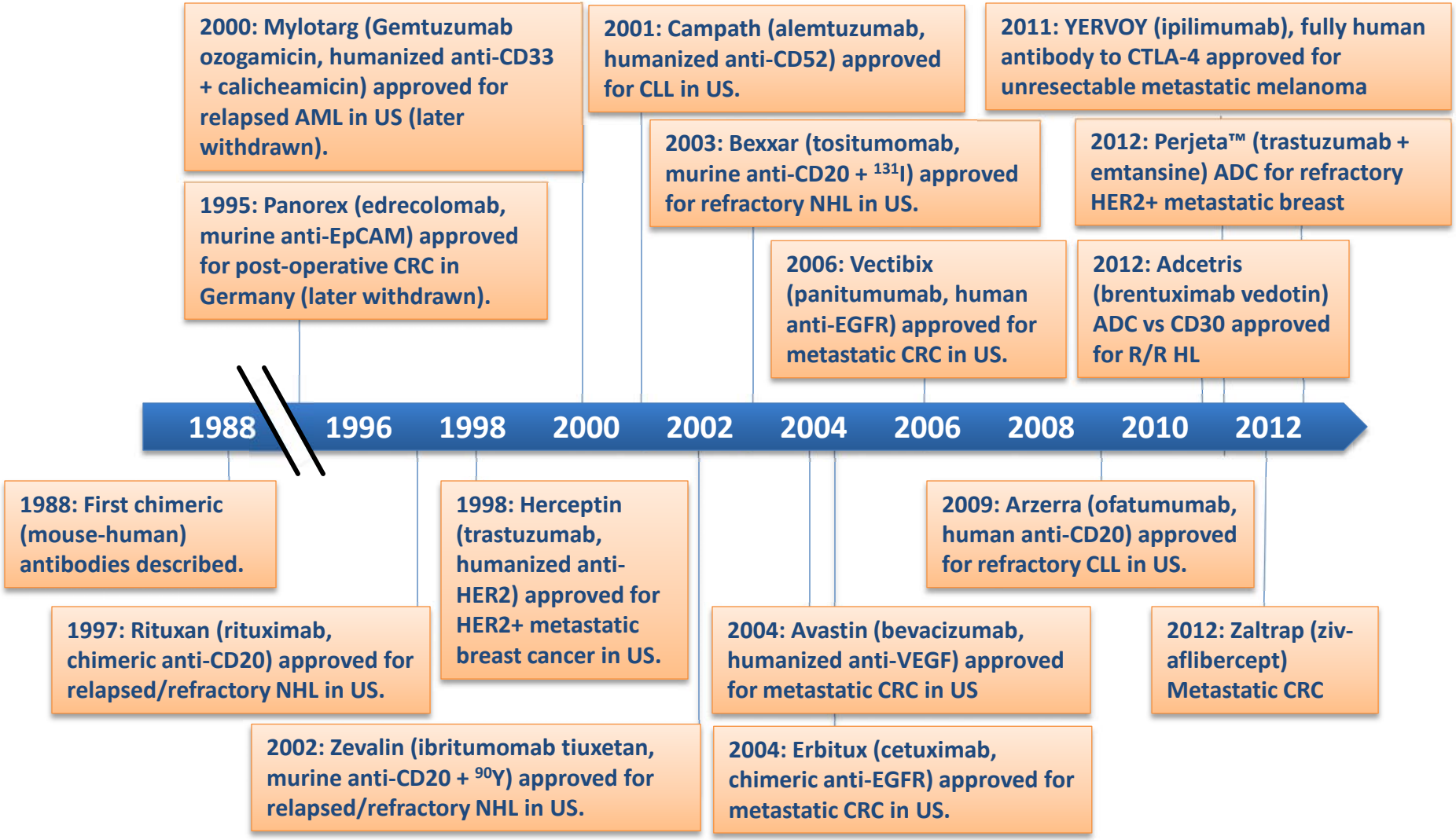
Moderator: Mike Rice, Senior Consultant, Defined Health

Panelists:

- Christian Zahnd, PhD, Chief Executive Officer, Molecular Partners AG
- John Haurum, MD, Chief Executive Officer , F-Star
- Hans-Peter Gerber, PhD, Executive Director, Pfizer
- John M. Lambert, Ph.D, Executive Vice President & Chief Scientific Officer, ImmunoGen, Inc.
- Bill Grossman MD, PhD, Senior Vice President of Research & Development, Biothera

CANCER PROGRESS by Defined Health

Cancer Has Been the Leading Indication for Novel Antibody Technologies



Biologics Comprise Significant Share of Top 10 Oncology Blockbusters - Forecasted to Exceed $22.5B by 2018

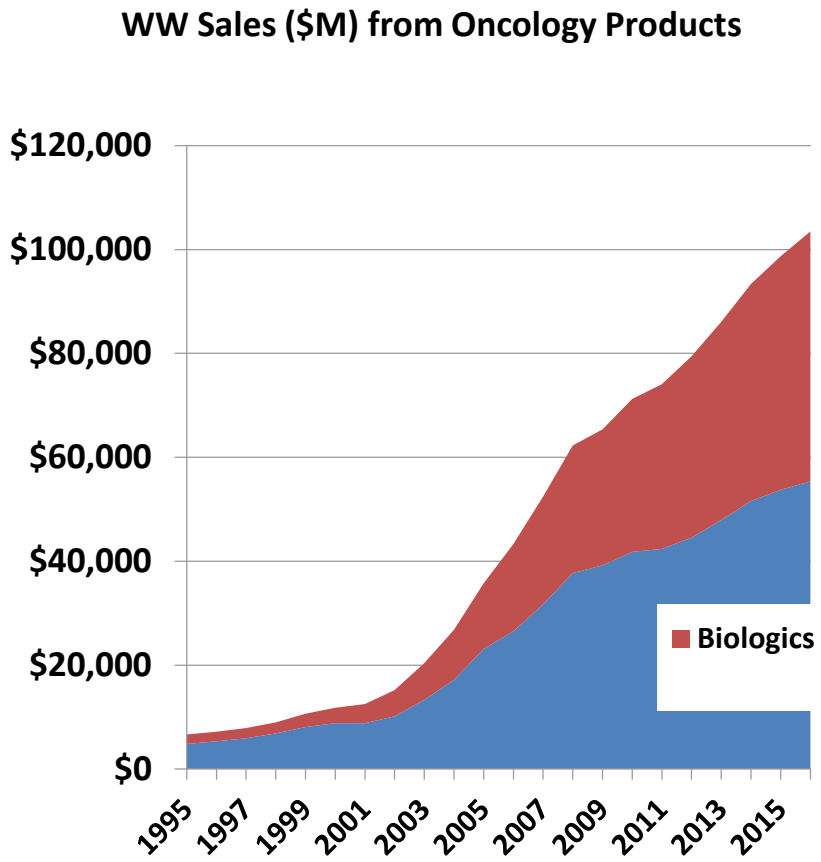
Top Ten Oncology Blockbusters are Expected to Grow 26% Over the Next Five Years

2018 Top 10 Cancer Drugs ($41.3B)				
Product	Company	Class	Patent Expiry	Revenue 2018 ($B)
Avastin	Roche	VEGF MAbs	2018	$7.6
Revlimid	Celgene	IMID	2026	$6.7
Rituxan	Roche	CD20 MAbs	2018	$6.3
Herceptin	Roche	HER2 MAbs	2019	$5.6
Perjeta	Roche	HER2 MAbs	--	$3.0
Xtandi	Astellas	AR Inhibitor	2027	$2.9
Afinitor	Novartis	MTOR Inhibitor	2019	$2.8
Tasigna	Novartis	Abl/c-Kit Inhibitor	2023	$2.5
Sprycel	BMS	Abl/SRC/c-Kit Inhibitor	2020	$2.0
Alimta	Eli Lilly	Antimetabolites	2017	$1.9

Evaluate Pharma

Biologics Are the Main Driver for Oncology Revenue in the Next Six Years

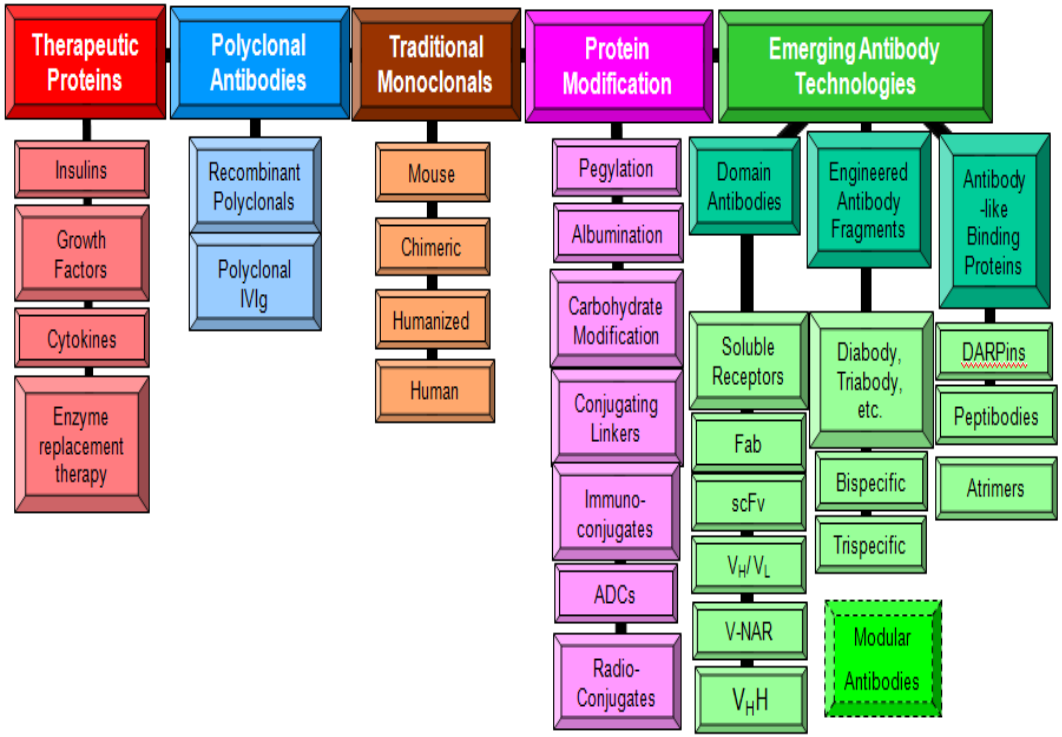
- Biologic drugs account for 40% of the oncology market today, increasing to 46% by 2016.
- During this forecast period, growth in biologics is forecast at 7% annually.
- Similar growth is expected for conventional small molecules as a whole, but certain categories- e.g. cytostatics and anti-angiogenics- are forecast to experience 15% growth during this period.



Source: EvaluatePharma

As Recombinant Technologies Increased in Sophistication, Biologic Platforms Became Increasingly Versatile

- The next gen platforms include improving on antibodies (such as via Potelligent technology to improve ADCC) or creating fragments or deriving antibodies from other species where size, CGS and IP issues underpin the rationale.
- One recent push has been around novel, non-antibody scaffolds, but while these offer theoretical benefits they are not yet validated and often lack key aspects such as Fc region and hence require pegylation or other half-life extending technology and lose effector function that has been shown to be an important part of most anticancer monoclonals.
- Another of the recent focuses for the past few years has been on multivalency, allowing the antibody (or other biologic) to hit more than one target, either multiple epitopes on the same cell surface molecule or distinct molecular targets.



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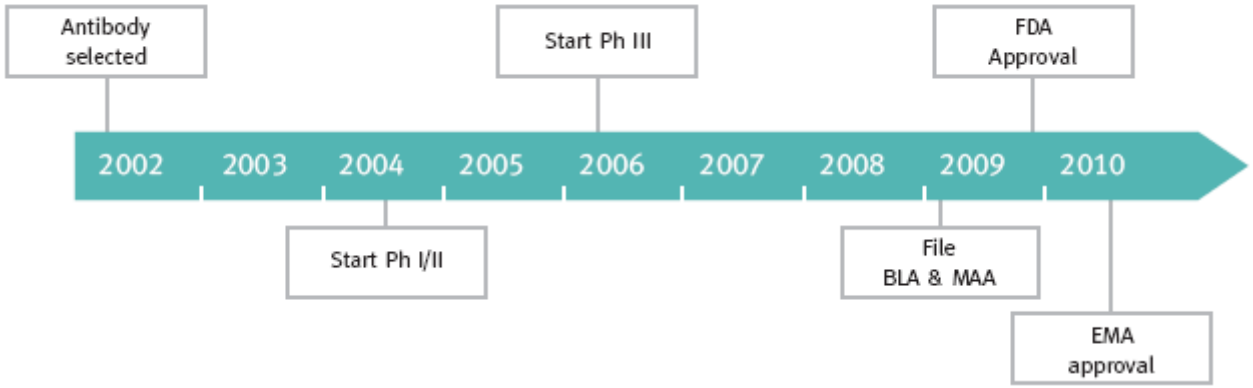
Technologies Employed In Improving The Product Profile Range From Subtle To More Radical Changes To The Reference Product

Technology	Activity/Value	Challenges	Development	Pharma Interest
Naked Antibodies	• Validated technology • No conjugation (bio)chemistry required	• Production costs • MOA optimization	Multiple marketed products	Multiple
Glycosylation	• Improved efficacy of existing mAbs	• Complicated biochemistry • Immunogenicity	Phase 3	Roche, others earlier
Antibody-Drug Conjugates	• Potency of small-molecules combined with specificity of mAbs	• Linker chemistry • Choice of small molecule	Multiple phase 3 products	Roche, Pfizer, Takeda
Antibody-directed enzyme prodrug therapy (ADEPT)	• ADC with a weakly toxic prodrug is selectively activated into a toxic agent at the tumor site • Selectivity is achieved by the tumor specificity and differential between tumor and normal tissue enzyme levels.	• Must remain on the cell surface to activate the circulating produg. • Must be rapidly cleared from circulation, which can be accomplished by mannose glycosylation of the mAb.	Cancer Research UK is currently investigating several ADEPT products (MFE-CP1 + ZD-2767-P) in solid tumors	Unknown
Antibody–cytokine fusion proteins	• Similar to conjugated molecule combined with specificity of mAbs • Antibodies fused to IL-2, GM-CSF, IL-12, TNFa, interferon, and other cytokines.	• Linker chemistry • Choice of toxin	One phase 2 product (tucotuzumab celmoleukin)	Merck-Serono
Bi-Specific Abs Modular Antibodies	• Increased and diversifiable payload	• Low production yield • Stability	One launched product (Removab)	None

Ofatumumab (Arzerra, Genmab/GSK) Is A Precedent For Clinical Development Biobetter CD20 Antibodies

- Ofatumumab is a fully human monoclonal CD20 biobetter antibody which inhibits early-stage B lymphocyte activation.
- Genmab states that is took only 2 years time from antibody selection to filing an IND to enter clinical development.
- In 2009, It was FDA approved for treating CLL that is refractory to fludarabine and alemtuzumab and has also shown potential in treating follicular Lymphoma, DLBCL, rheumatoid arthritis and relapsing remitting multiple sclerosis.
- Ofatumumab has also received conditional approval in Europe for the treatment of refractory chronic lymphocytic leukemia. This makes ofatumumab the first marketing application for an antibody produced by Genmab, as well as the first human monoclonal antibody which targets the CD20 molecule that will be available for patients with refractory CLL.

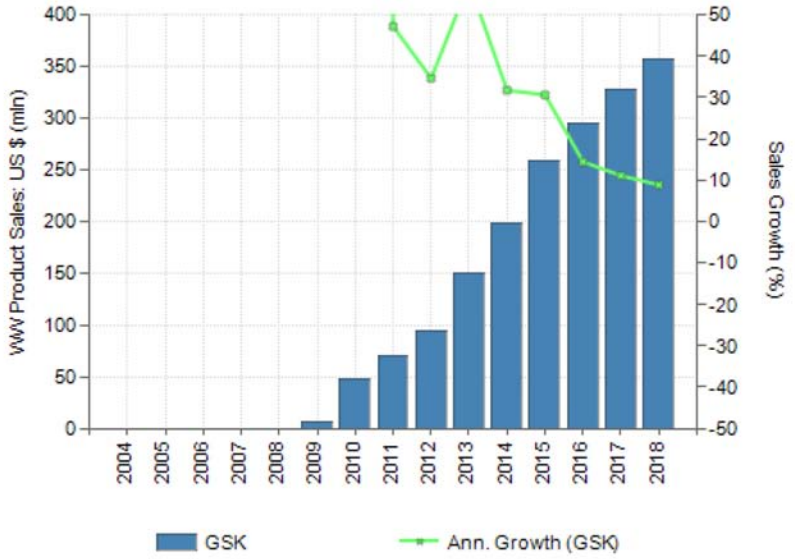


Genmab 2010 Annual Report

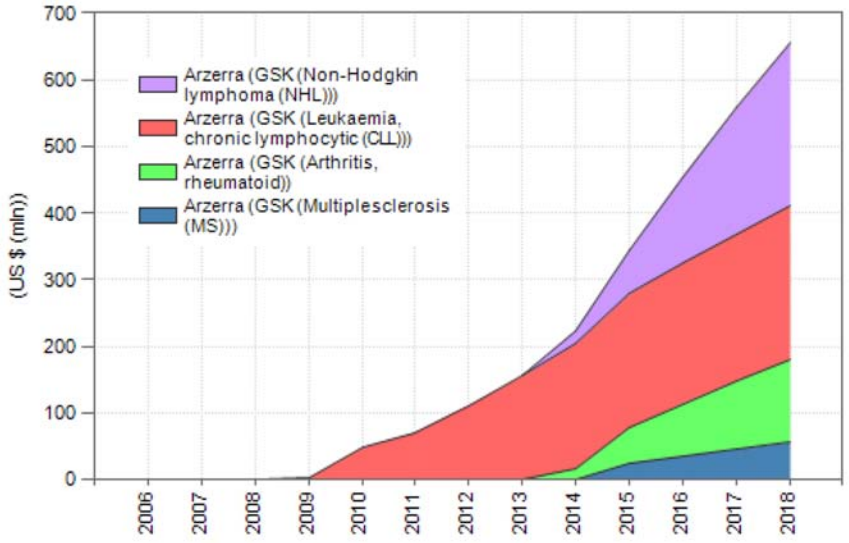
Arzerra Sale Demonstrates the Commercial Challenges For Incrementally Advanced Monoclonals In The Oncology Market

Arzerra Displays Higher CD20 Affinity And Enhanced ADCC And CDC, But Lack Of True Clinical Differentiation & Accumulated Data For First-in-Class Rituxan Serve As A Barrier That Has Limited Sales

Ofatumumab (*Arzerra*, GSK) Projected Overall WW Sales



Ofatumumab (*Arzerra*, GSK) Projected WW Sales Revenue By Indication



Estimated WW *Arzerra* Revenue By Indication

Many Other CD20 Follow-ons Are In Development, But It Is Unclear If Any Will Yield Clinically Differentiated Products For NHL/CLL

- Since the approval of rituximab in 1997, two anti-CD20 mAbs with radioactive payloads have been approved, and GSK/Genmab's Arzerra (ofatumumab) which received accelerated approval for use in patients with chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab.
- There are over 20 CD20 novel and biosimilar antibody programs in clinical development WW and over 40 in discovery stage.

mAb	Format	Indication	Manufacturer	Binding site	Comments	Phase Dev
Rituximab Rituxan* MabThera*	cIgG1	NHL, RA	Genentech, Biogen	Type I	PCD, ADCC, CDC, ADCP	Approved in US 1997
Reditux	cIgG1	NHL	Dr. reddy Laboratories	Same as Rituximab	Biosimilar	Approved in india 2007
Y90-ibritumomab tiuxetan Zevalin*	mIgG1	NHL	Biogen IDEC	Same as Rituximab	Low ADCC	Approved in US 2002
I131tositumomab Bexxar*	mIgG2a	NHL	GlaxoSmithKline	Different than Rituximab Type II	Low CDC	Approved in US 2003
Ofatumumab Arzerra*	hIgG1	CLL, NHL, RA	Genmab, GlaxoSmithKline	Different than Rituximab	Low K_{off} High CDC	Approved in US 2009
Ocrelizumab	hIgG1	NHL, RA	Genentech, Roche, Biogen	Same as Rituximab	High ADCC Low CDC	Phase 3
Veltuzumab	hIgG1	NHL, ITP	Immunomedics	Same as Rituximab	Low K_{off} High CDC	Phase 2
Obinutuzumab GA101	hIgG1	CLL, NHL	Glycart Roche	Type II	High PCD High ADCC Low CDC	Phase 2
AME-133v	hIgG1	NHL	Applied Molecular Evolution, Eli Lilly	N/A	High ADCC	Phase 2
TRU-015	SMIP	RA	Trubion Pharma, wyeth	N/A	High ADCC Low CDC	Phase 2
PRO131921 (Version 114)	hIgG1	CLL, NHL	Genentech	N/A	High CDC High ADCC	Phase 1/2
LFB-R603/EMAB-6	cIgG1	CLL	GTC Biotherapeutics, LFB Biotechnologies	N/A	High ADCC	Phase 1

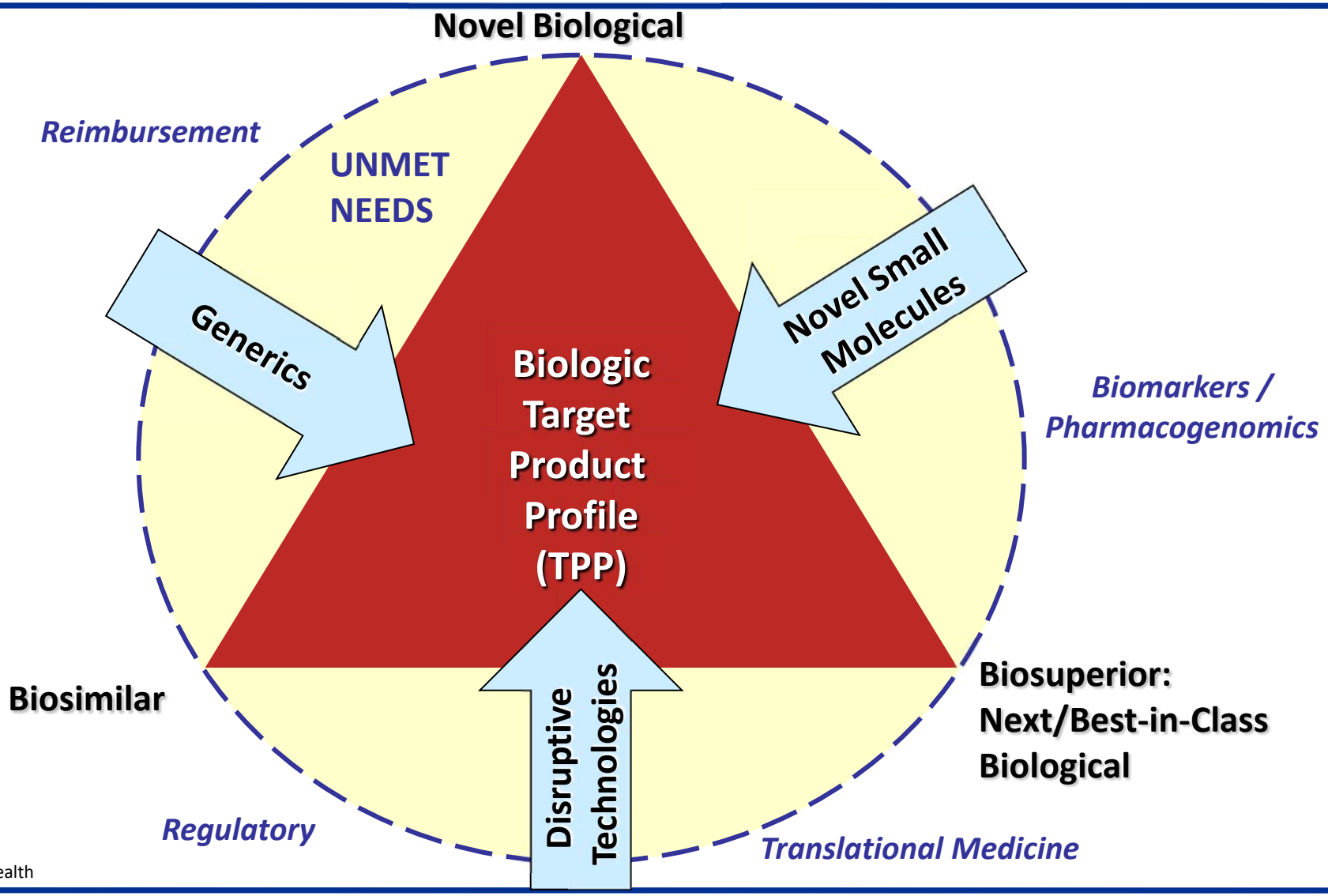
MAbs. 2010 Jan-Feb; 2(1): 14–19; Haematologica. 2010; 95:135-143.

Emerging Markets Already have Access to Rituximab Biosimilars – Numerous Rituximab Biosimilar Products Heading For US Market

Drug	Originator	Phase
obinutuzumab	Glycart Biotechnology AG	Phase 3 Clinical
rituximab biosimilar, BI	Boehringer Ingelheim Corp	Phase 3 Clinical
ocaratuzumab	Applied Molecular Evolution Inc	Phase 3 Clinical
ocrelizumab	Genentech Inc	Phase 3 Clinical
veltuzumab	Immunomedics Inc	Phase 2 Clinical
ublituximab	LFB Biotechnologies	Phase 2 Clinical
rituximab biosimilar, Pfizer	Pfizer Inc	Phase 2 Clinical
BVX-20-CD20	Vaccinex Inc	Phase 1 Clinical
rituximab biosimilar, Merck	Merck & Co Inc	Phase 1 Clinical
64Cu-DOTA-rituximab	Stanford University	Phase 1 Clinical

Drug	Originator	Phase
rituximab biosimilar, iBio/Fraunhofer USA	iBio Inc	Discovery
rituximab biosimilar, Oncobiologics/Parilis	Oncobiologics Inc	Discovery
rituximab biosimilar, PanPharmaceuticals	Harvest Moon Pharmaceuticals USA Inc	Discovery
rituximab biosimilar API	Therapeutic Proteins Inc	Discovery
rituximab biosimilar, Coherus BioSciences	Coherus / Daiichi Sankyo	Discovery
rituximab biosimilar. Actavis/Amgen	Amgen Inc	Discovery
rituximab biosimilar, Lentigen	Lentigen Corp	Discovery
rituximab follow-on biologic, LFB/rEVO	rEVO Biologics	Discovery
rituximab biobetter, Caliber	Caliber Biotherapeutics	Discovery
rituximab biosimilar, Viropro/Spectrum	Viropro Inc	Discovery

However, all biologics face increasing pressure on TPPs



Source: Defined Health

Discussion Points

- Opportunity for multi-specific biologics: Targeting multiple pathways in cancer for efficacy and to subvert resistance.
- How to choose and how to prioritize targets, for naked and for ADC approaches
- Orthogonal approaches and how to be agnostic/unbiased to the best way forward (e.g., separate combinations of products versus multi-specifics), what data drives the key decision?
- How to best study combinations with SOC regimens as well as other agents
- Extending this, how to determine best approach of a biologic or ADC versus SMI for a given cancer situation, for companies with both toolkits
  - Weighing the scientific and commercial issues in such decision-making
  - Biomarkers and predictive preclinical models for enabling decisions
- Increasing pressure for substantive, not incremental, improvement and implications to building bringing products forward
  - Scientific rationale, clinical path forward (patient settings), TPPs
  - differentiation from first-in-class marketed products and from related pipeline
  - Impact of biosimilars (versus biosuperiors).

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