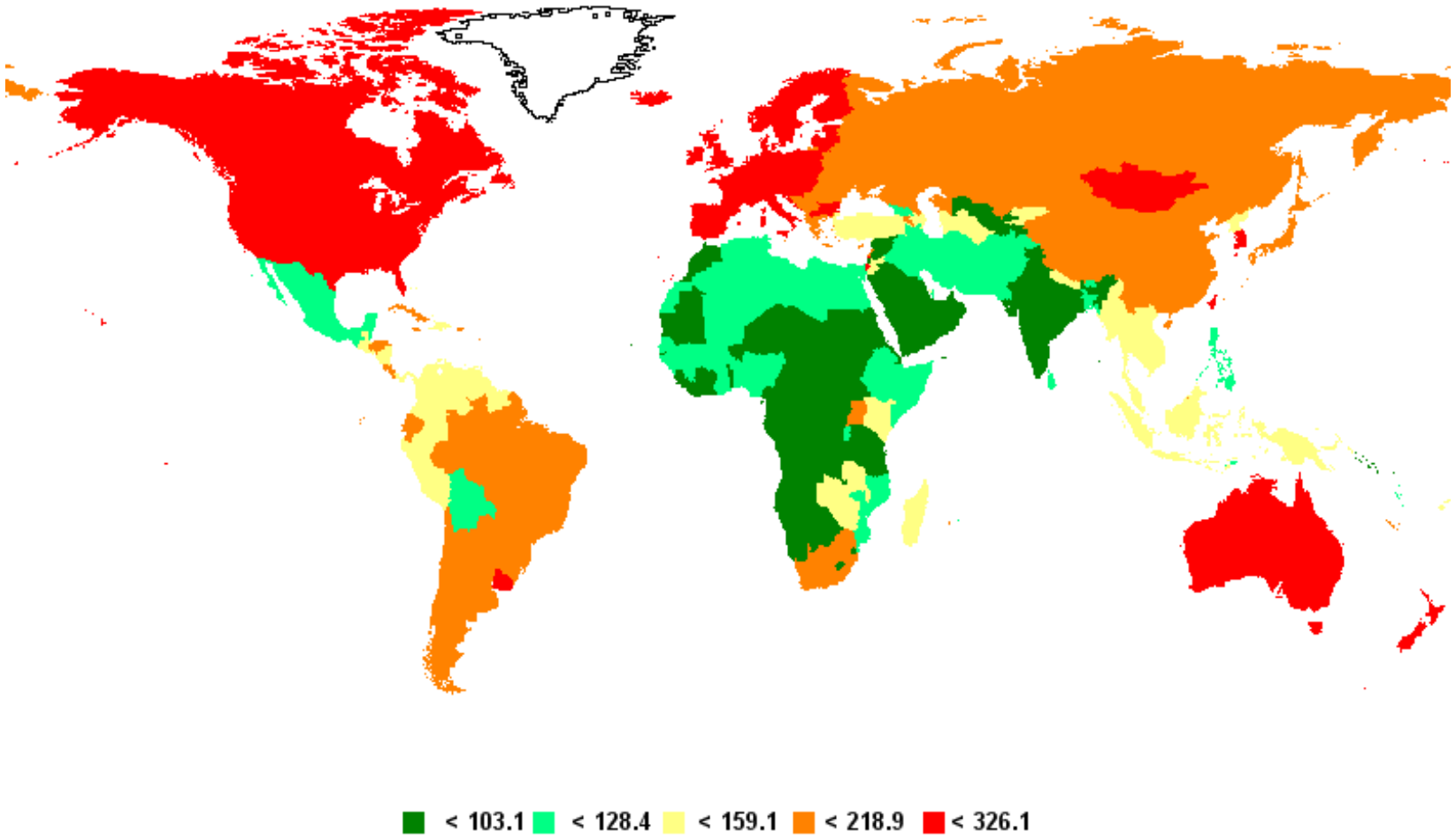

Среда 22 мая 16:00
Конференц-зал ИЦИГ
Публичная лекция
Вячеслава Власова
"Рак и лекарства:
есть ли свет в конце туннеля?"

Cancer statistics

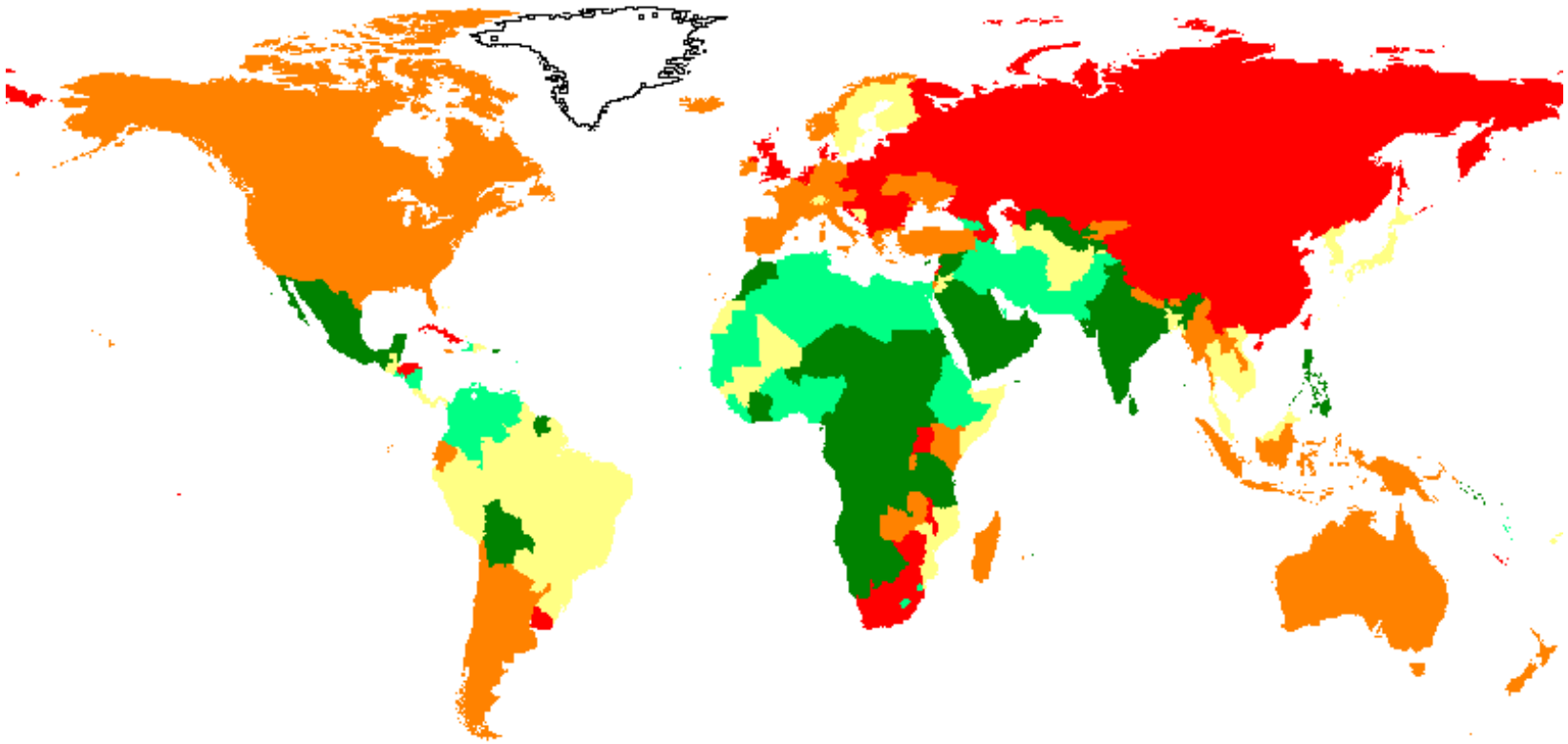
- 12 million people diagnosed each year
- 8 million people die each year from cancer
- Cancer is on increase mostly due to growing and ageing population

Estimated age-standardised incidence rate per 100,000
All cancers excl. non-melanoma skin cancer: both sexes, all ages



GLOBOCAN 2008 (IARC) - 16.5.2013

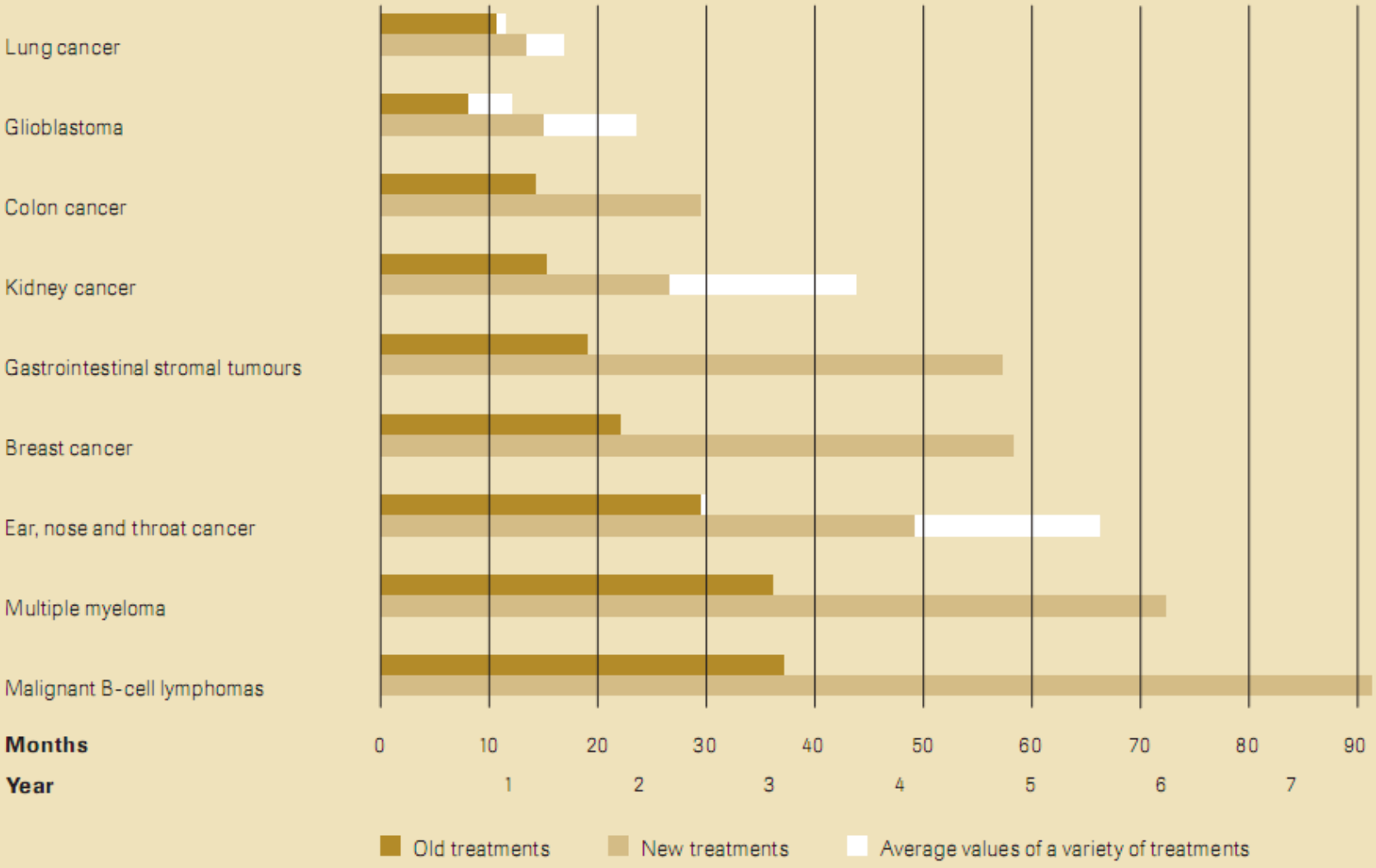
Estimated age-standardised mortality rate per 100,000
All cancers excl. non-melanoma skin cancer: both sexes, all ages



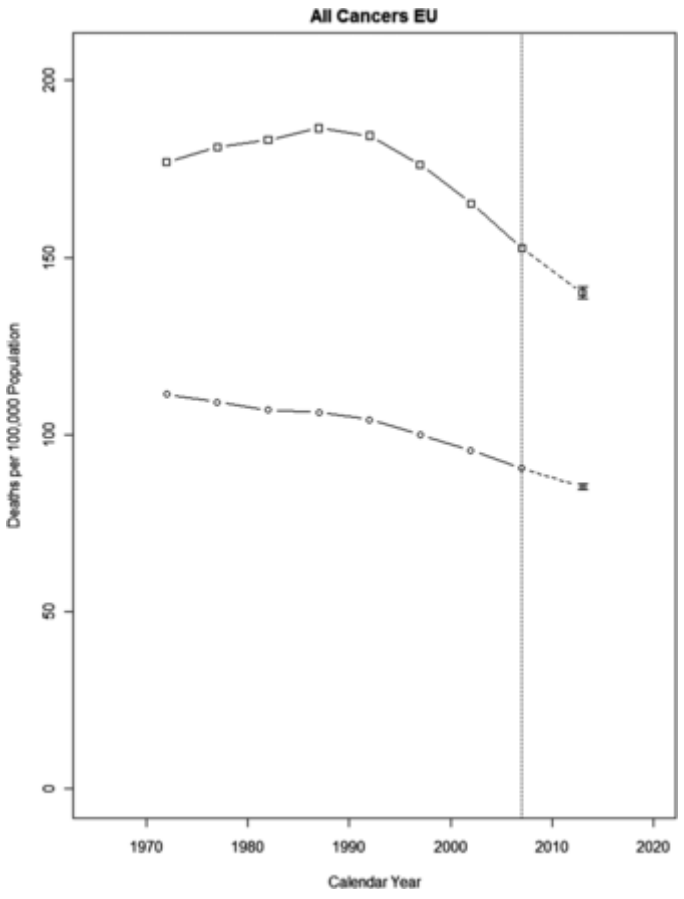
< 79.3 < 89.2 < 101.4 < 114.9 < 185.2

GLOBOCAN 2008 (IARC) - 16.5.2013

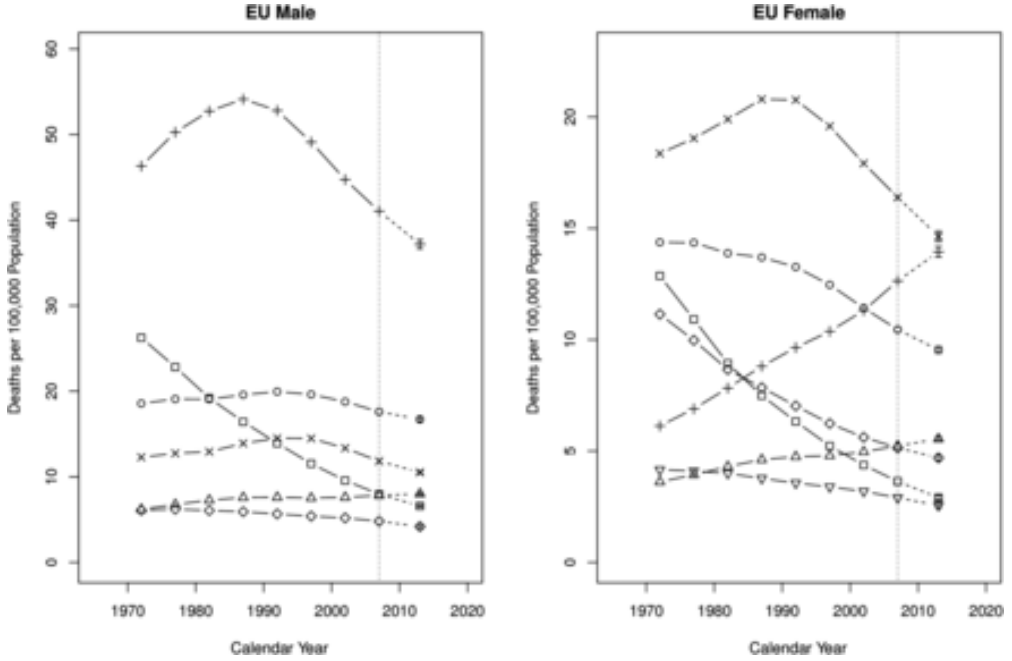
Progression of overall survival (average in months) in advanced cancers in the last decade



Cancer mortality trends from 1970–1974 to 2005–2009 and the predicted rates for 2013 in the EU



Squares - men, circles - women



Men: stomach (squares), intestines (circles), pancreas (triangles), lung (crosses), prostate (xs) and leukemias (diamonds). Women: stomach (squares), intestines (circles), pancreas (triangles), lung (crosses), breast (xs), uterus (diamonds) and leukemias (inverted triangles)

Malvezzi, M. et al. (2013) European cancer mortality predictions for the year 2013. Annals of Oncology doi: 10.1093/annonc/mdt010

Why so little progress?

- Profit structure in industry
- Lack of financial resources
- Adverse regulatory environment
- Problems of early diagnostics
- Very few really effective new drugs
- Prohibitive cost of treatments
- Disconnect between patients, doctors and science

CHANGE TEXT SIZE

AUTHOR

Sharon Begley

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In Newsweek Magazine

We Fought Cancer…And Cancer Won.

Sep 5, 2008 8:00 PM EDT

After billions spent on research and decades of hit-or-miss treatments, it's time to rethink the war on cancer.

There is a blueprint for writing about cancer, one that calls for an uplifting account of, say, a woman whose breast tumor was detected early by one of the mammograms she faithfully had and who remains alive and cancer-free decades later, or the story of a man whose cancer was eradicated by one of the new rock-star therapies that precisely target a molecule that spurs the growth of malignant cells. It invokes Lance Armstrong, who was diagnosed with testicular cancer in 1996 and, after surgery and chemotherapy beat it back, went on to seven straight victories in the Tour de France. It describes how scientists wrestled childhood leukemia into near submission, turning it from a disease that killed 75 percent of the children it struck in the 1970s to one that 73 percent survive today.

But we are going to tell you instead about Robert Mayberry. In 2002 a routine physical found a lesion on his lung, which turned out to be cancer. Surgeons removed the malignancy, which had not spread, and told Mayberry he was cured. "That's how it works with lung cancer," says oncologist Edward Kim of the University of Texas M. D. Anderson Cancer Center in Houston, who treated Mayberry. "We take it out and say, 'You're all set, enjoy the rest of your life,'

Adams, D.J. (2012) *Trends in Pharmacological Sciences* 33, 173-180.

Opinion

The Valley of Death in anticancer drug development: a reassessment

David J. Adams

Department of Medicine, Duke University Health System, Duke Box # 2638, Research Drive, Durham, NC 27710, USA

The past decade has seen an explosion in our understanding of cancer biology and with it many new potential disease targets. Nonetheless, our ability to translate these advances into therapies is poor, with a failure rate approaching 90%. Much discussion has been devoted to this so-called 'Valley of Death' in anticancer drug development, but the problem persists. Could we have overlooked some straightforward explanations to this highly complex problem? Important aspects of tumor physiology, drug pharmacokinetics, preclinical models, drug delivery, and clinical translation are not often emphasized, but could be crucial. This perspective summarizes current views on the problem and suggests feasible alternatives.

[15], the concept is not routinely incorporated into preclinical models. A central issue is the definition of 'normoxia'. Normoxia is often equated with the ambient air found in tissue culture incubators. However, no tissue in the body is exposed to 20–21% oxygen, and instead tissue levels can range from zero in bone marrow to 14% in well-perfused organs (lung, liver, kidney, heart) with circulating levels of 10–12% [16,17]. Human solid tumors are typically hypoxic at 0–5% O_2 [18]. Low levels of oxygen can induce stabilization of the transcription factor hypoxia-inducible factor 1 α (HIF-1α), which upregulates over sixty genes, including those controlling the glycolytic phenotype that produce lactate-mediated extracellular acidification [19,20]. Thus, gene-expression profiles are very different under hypoxia versus the standard hyperoxic conditions of traditional *in*

Table 1. Reported factors that contribute to the Valley of Death in anticancer drug development

Factor	Cause(s)	Ref
Lack of efficacy and safety	Lack of predictive animal models and strong evidence for mechanism of action (MOA)-based efficacy; failure to eliminate compounds with MOA-based toxicity; increasing safety hurdles; poor pharmacokinetics	[3,4,14,40]
Lack of financial resources	Risk-averse mentality at the National Institutes of Healthy (NIH), pharma, venture capital; majority of NIH support funds basic research, less than 5% for translational research	[4–6]
Lack of human resources	Consolidation in pharmaceutical industry; >35 000 jobs lost in 2010 alone	[5,102,103]
Lack of required research structure	Individual investigator model versus multidisciplinary team	[5]
Lack of support expertise	Different support and management structures for basic versus translational and clinical research	[5]
Communication	Poor communication between clinical and basic scientists and between scientists and the business community	[5]
Design of clinical trials	Lack of medically and statistically meaningful endpoints; lack of and failure to incorporate validated biomarkers; lack of appropriate patient selection; lack of pharmacokinetic guidance	[7,14,104,105]
Healthcare culture	Failure to adopt results from clinical studies into clinical practice	[106]
Lack of incentives in academia	Reward/promotion structure in academia; difficulty in assessing outcomes of translational research to reward effort	[5]
Profit structure in industry	Large pharma seeks blockbuster drugs in large markets versus orphan drugs; pressure from Wall Street for short-term profits	[9,107]
Focus on high risk diseases	Trade-off high potential profits for high attrition rate; compounds with novel MOAs have higher attrition rates	[1,14,108]
Focus on technology	Human genome project has generated unlimited potential targets, but few have been validated	[102]
Choice of drug type	Focus is on small molecules whereas biologicals have higher rates of success	[14]
Lack of predictive discovery models	Current target-centric approach; many targeted agents affect essential cellular functions and behave similarly to cytotoxics	[104,109]
Lack of predictive development models	Failure to capture tumor heterogeneity and cellular complexity; inadequate understanding of pathway connectivity in tumor versus normal cells; limited support for clinically relevant model development	[2,108]
Adverse regulatory environment	Initial clinical experience is in patients with advanced, refractory disease; inadequate funding of regulatory agencies such as the FDA; lack of global regulatory harmonization	[2,9,110]
Intellectual property issues	Limited patent lifetime relative to the extended development time; overarching patents that restrict research in key fields	[111]
Aggressive pricing may create barriers to reimbursement	High attrition rates amplify costs of drug development that are passed on to patients	[2,107]
Lack of innovation	Pipelines all focus on a limited number of mechanisms and targets; lack of compelling new biology, enabling technologies, genomics-derived tumor-specific targets, and therapeutic concepts	[3,110]
Feasibility and cost of manufacture and development	Complex drug molecules or drug carriers; overall cost to bring NME to market now estimated at $1 billion	[3,7]
Commercial issues	Alignment of corporate R&D with marketing goals; awareness of competitor programs; over-management of R&D by those lacking scientific-medical expertise; resources focused on marketing	[14,107]

What should be done?

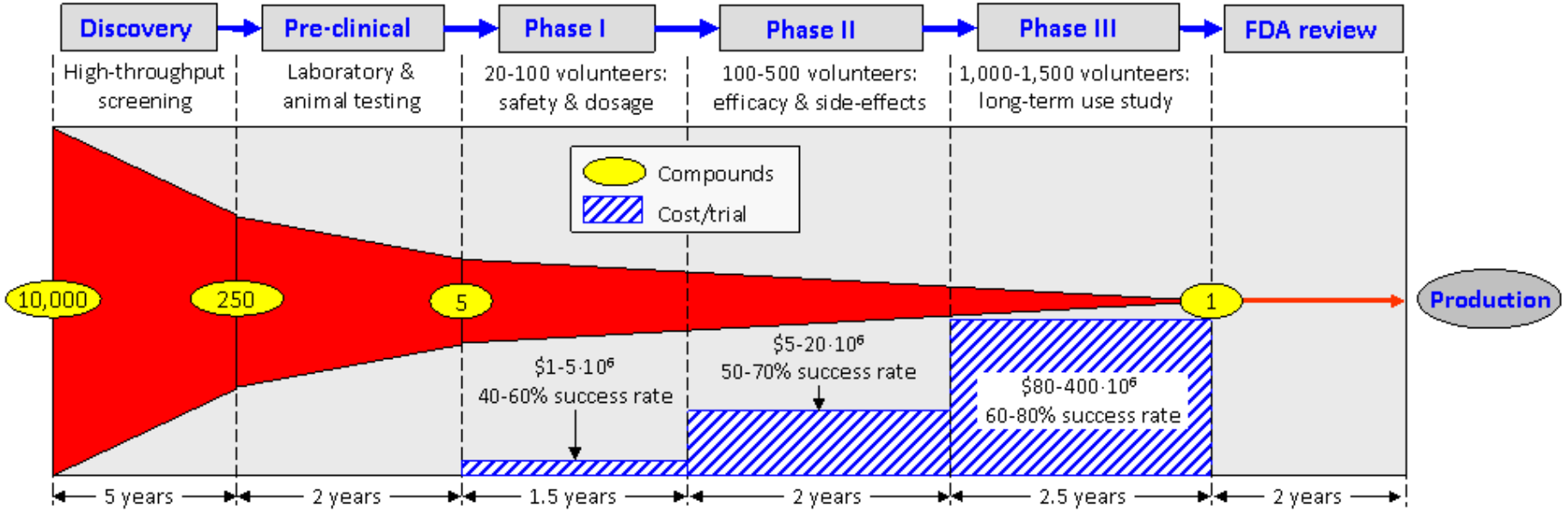
- Prevention
- Early detection
- Effective primary treatment
- Post-treatment monitoring
- Handling of recurrent and resistant disease

Financial reports as windows into the near future

- Financial reports are some of the most reliable sources of information about drugs under development
- Four most frequent cancer will be analysed (lung, breast, prostate, colorectal)
- Top 20 pharmaceutical companies included in the analysis

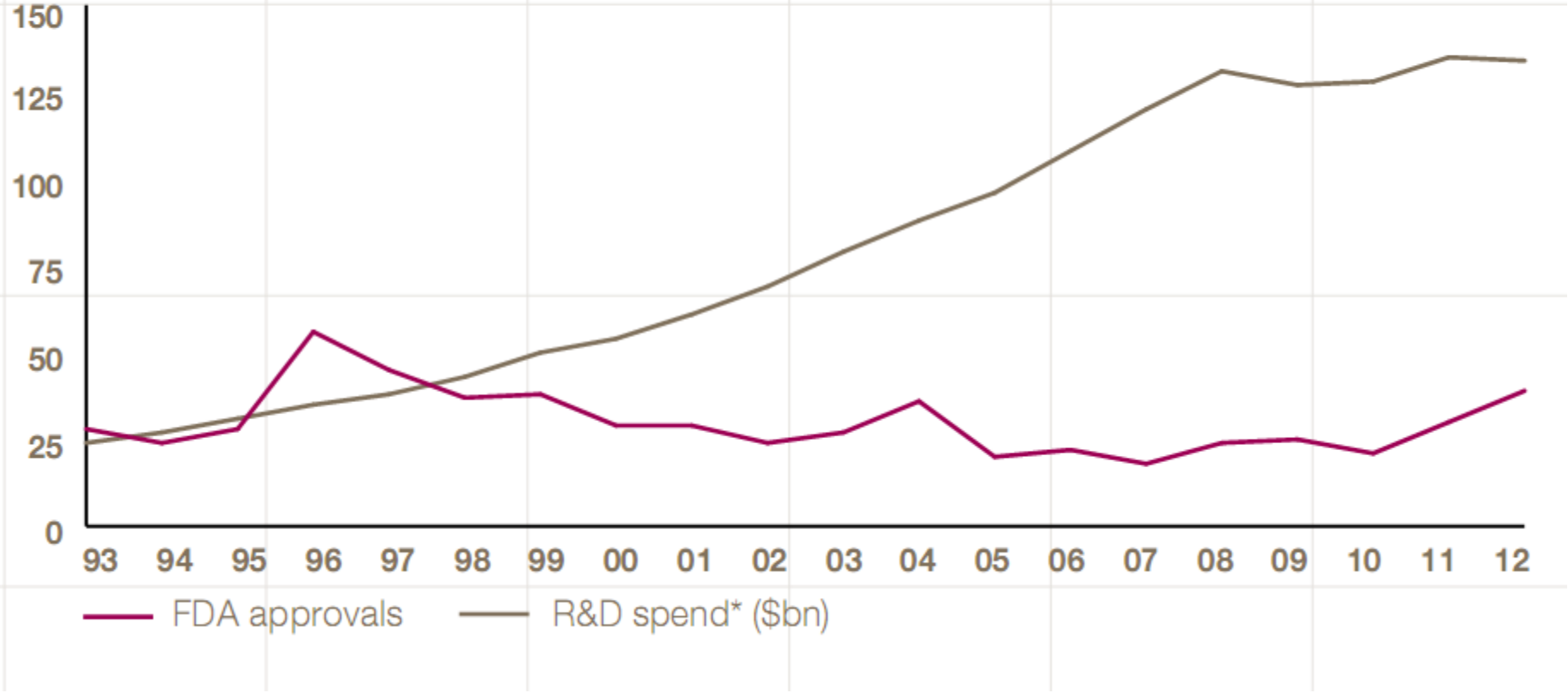
	Company	Revenue in US$ mln
1	Pfizer	$57,747
2	Novartis	$47,935
3	Sanofi	$42,779
4	Merck	$41,289
5	GlaxoSmithKline	$35,594
6	AstraZeneca	$32,981
7	Johnson & Johnson	$24,368
8	Eli Lilly & Co.	$22,608
9	Abbott Laboratories	$22,435
10	Bristol-Myers Squibb	$21,244
11	Takeda Pharma	$17,257
12	Teva	$16,689
13	Boehringer-Ingelheim	$14,058
14	Bayer Schering	$13,853
15	Astellas	$12,311
16	Daiichi-Sankyo	$11,338
17	Otsuka Pharmaceutical	$9,935
18	Gilead Sciences	$8,102
19	EISAI	$7,710
20	Mylan	$6,106

Pharmaceutical research and development pipeline



Cost of successful drug development – US$1.3 bn.
Cancer drugs cost 20% more.
Only large companies with capitalization level in billions US$ have realistic chances to deliver new treatments.
Only clinical trials stage III drugs or filed drugs considered.
67% of stage III anticancer drugs fail → drugs at stages I and II not included in the analysis.

R&D productivity



Lung cancer (19 compounds)

Drug	Phase	Molecular Target	Company	Info
Dacomitinib	3	Pan-HER inhibitor	Pfizer	Previously treated advanced NSCLC
Xalkori (crizotinib)	Appr.; 3	c-MET/ALK inhibitor	Pfizer	Approved for ELM4-ALK fusion gene carriers (4% of LC cases); ALK-positive 1st and 2nd line NSCLC
Motesanib	3	Antagonist of VEGFR 1-3, PDGFR, and SCFR.	Amgen	1st line NSCLC
Nintedanib	3	Anti-vascular agent (inhibitor of VEGFR, FGFR and PDGFR)	Boehringer Ing.	2nd line NSCLC (trials LUME-Lung 1 and LUME-Lung 2)
Yervoy	3	Immunotherapeutics: CTLA-4	BMS	1st line squamous NSCLC
Nivolumab	3	Immunotherapeutics: Anti-PD-1, reactivation of T cells	BMS	
Necitumumab	3	Antibody, inhibitor of EGFR	Eli Lilly	Advanced Squamous NSCLC, 1st line
Ramucirumab	3	Antibody to extracellular domain of VEGF receptor -2 (blocks interactions with ligands and angiogenesis)	Eli Lilly	
Tasisulam	3 (?)	Induction of apoptosis by activating the mitochondrial cell death pathway	Eli Lilly	NSCLC, Suspended for metastatic melanoma

Full table: www.wlassoff.com

Lung cancer

Target	Number of companies working on this target
VEGFR	4
EGFR (HER-1)	3
c-Met (HGFR)	3
PDGFR	2
SCFR	1
FGFR	1
PARP	1
Clusterine	1
Microtubules	2
Immunotherapeutic targets (CTLA-4, PD-1, MUC-1)	2

(GF, receptors and corresponding TKs considered as single target)

Prostate cancer

Drug	Phase	Molecular Target	Company	Info
Xgeva	3 Appr.	Antibody, receptor activator for nuclear kappa (RANK) ligand	Amgen GSK	Delay or prevention of bone metastases in prostate cancer
Radium-223 dichloride	Filed		Bayer	Hormone refractory prostate cancer with bone metastases
Yervoy	3	Immunotherapeutics: CTLA-4	BMS	Post hormonal, post chemotherapy
Zytiga	Appr.	17,20 lyase	Johnson and Johnson	Castration resistant, chemo naive
TAK-700 (orteronel)	3	Non-steroidal androgen synthesis inhibitor (17,20 lyase)	Takeda	
TAP-144-SR (leuprorelin acetate)	3	LH-RH agonist (GnRH receptor)	Takeda	Approved in Japan, Europe, Asia
Degarelix	Appr.	GnRH antagonist	Astellas	
Custirsen (OGX-011/TV-1011)	3	Inhibitor of clusterin production, antisense drug	Teva	Metastatic castration-resistant PC

Prostate cancer

Target	Number of companies working on this target
RANK	1
17,20 lyase	2
GnRH receptors	2
Clusterin	1
Immunotherapy (CTLA-4)	1

Colorectal cancer

Drug	Phase	Molecular Target	Company	Info
Vectibix	3	antibody to EGF receptors	Amgen	1st and 2nd line colorectal cancer
Nintedanib	2	Anti-vascular agent (inhibitor of VEGFR, FGFR and PDGFR)	Boehringer Ing.	Metastatic bowel cancer
Regorafenib (stivarga)	Filed	Multi-kinase inhibitor (VEGFR2-TIE2 tyrosine kinase)	Bayer	Metastatic colorect. cancer
Ramucirumab	3	Antibody to extracellular domain of VEGF receptor -2 (blocks interactions with ligands, and angiogenesis)	Eli Lilli	
Erbitux (Cetuximab)	Approved 2012	Anti-EGFR mAb	Merck	Metastatic colorect. cancer (KRAS wild-type)
Avastin	Filed	mAb to VEGF-A	Roche	mCRC TML (extends OS)
Zaltrap	Approved 2012	Angiogenesis inhibitor, VEGF-A and VEGF-B	Sanofi Aventis	mCRC, OS increased by 1.5 months, RFS by 2.2 months
Erlotinib (Tarceva)	3	HER1/EGRF tyrosine kinase inhibitor	Astellas	
TAS-102	Filed; 3	Combination trifluridine and tipiracil (nucleoside analogues)	Otsuka	

Colorectal cancer

Target	Number of companies working on this target
VEGFR	5
EGFR	3
FGFR	1
PDGFR	1
TIE2	1
Thymidine phosphorylase	1

(GF, receptors and corresponding TKs considered as single target)

Breast Cancer (17 compounds)

Drug	Phase	Molecular Target	Company	Info
Xgeva	3 Appr.	Antibody, receptor activator for nuclear kappa (RANK) ligand	Amgen, GSK	Delay or prevention of bone metastases in breast cancer
Sorafenib	3	inhibitor of several Tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases (more avidly C-Raf than B-Raf)	Bayer	
Ramucirumab	3	Antibody to extracellular domain of VEGF receptor -2 (blocks interactions with ligands, and angiogenesis)	Eli Lilly	
Tasisulam	3 (?)	Induction of apoptosis by activating the mitochondrial cell death pathway	Eli Lilly	Suspended for metastatic melanoma
Tyverb/Tykerb (lapatinib)	3; Filed (for mBC)	Her2 and EGFR dual kinase inhibitor	GSK	Adjuvant therapy of breast cancer; metastatic breast cancer in combination with trastuzumab
Denosumab	3	Anti-RANKL antibody	Daiichi Sankyo	Adjuvant therapy
Afinitor	Approved (US, EU)	mTOR inhibitor	Novartis	Under devt. for HER2 positive breast cancer
BKM120	3	PI3K inhibitor	Novartis	Expected 2015
Trastuzumab Emtansine (T-DM1)	Filed	Antibody (trastuzumab, anti-HER2 Ab) -Cytotoxic drug (DM1) conjugate, one of the first drugs of this kind	Roche	HER2+ metastatic breast cancer, 2nd line (EMILIA trial successful – 32% lower risk of death, 6 months longer survival)

Breast cancer

Target	Number of companies working on this target
VEGFR	3
EGFR (HER-1)	1
HER2	3
RANK/RANKL	2
PDGFR	1
Raf kinases	1
mTOR	1
PI3K	1
GnRH receptors	1
Microtubules	1
Androgen receptors	1

(GF, receptors and corresponding TKs considered as single target)

General trends

- Popularity of certain targets: many companies work on the same or similar ideas
- Increasing attention to the late stage / metastatic disease
- 2nd line treatment: tackling of resistant and recurrent disease
- Combination therapies get developed: simultaneous attack on cancer cells, lower chances of resistance

Under-represented in the pipelines:

- Natural compounds/leads work better but the focus is still on small molecules
- Cytotoxic compounds are not fashionable

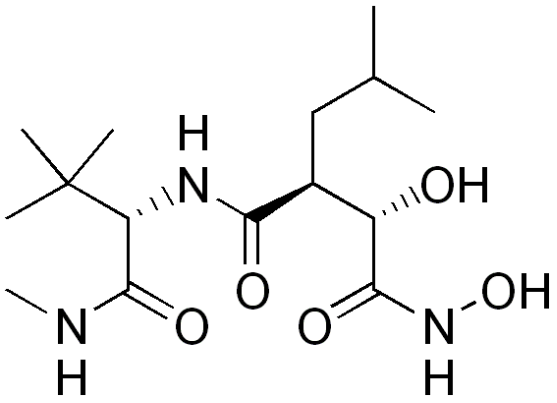
Where are the fruits of recent great ideas?

A bit of recent history

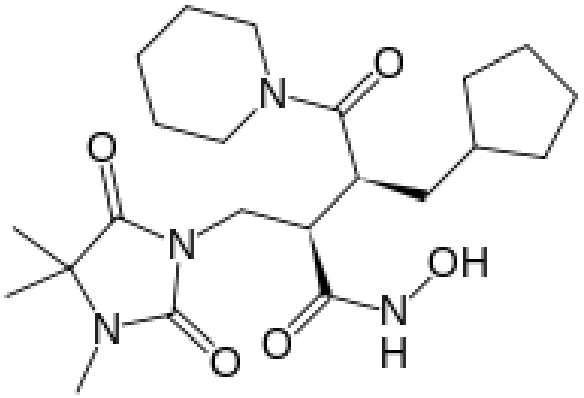
- MMP inhibitors (1990s): only few not particularly successful drugs
- Hypoxia-activated drugs
- Angiogenesis inhibitors
- Viral delivery vectors
- Each big idea has delivered some small improvements, but nothing revolutionary

MMP inhibitors

Matrix metalloproteinases are key enzymes in the development of metastases
MMP inhibitors were under development from 1990s



Merimastat



Cipemastat

JF Fisher (2006) Recent advances in MMP inhibitor design. Cancer Metastasis Rev 25: 115–136

Virus directed therapeutics

- Promising experimental results
- Limited success in humans
- Investor's mentality:

Some potentially big ideas

- Targeted delivery/activation (T-DM1 – approved in Feb 2013 for HER+ breast cancer; ADEPT)
- Immunotherapy (Yervoy – activates cytotoxic T-lymphocytes)
- Chemokine receptors and direction of metastatic spread
- Cancer stem cells
- Old techniques with big potential:

    - Photodynamic therapy (impressive results with lung mesothelioma)

    - Hyperthermia (excellent in combination with radiotherapy/chemotherapy)

Prevention

- Unhealthy lifestyle choices account for approximately 30% of all cancers
- Screening for genetic predisposition followed by regular monitoring or preventive measures

Culture › Film › Angelina Jolie

Angelina Jolie reveals she has had preventive double mastectomy

Actor reveals she has had mastectomy because of gene defect that increases risk of developing cancer that killed her mother

Jonathan Haynes
guardian.co.uk, Tuesday 14 May 2013 10.01 BST

Angelina Jolie, pictured in London on 11 April, underwent a preventative double mastectomy and reconstructive surgery that was completed on 27 April. Photograph: WPA/Getty Images

Early detection

- Breast cancer – mammography
- Prostate cancer – PSA (prostate specific antigen, potential of overtreatment)
- Colorectal cancer – CEA (carcinoembryonic antigen)
- Lung cancer - ???
- Breath tests might be the answer (stomach cancer breath tests already developed; use of sniffer dogs)
- Problem of overdiagnosis and incorrect diagnosis

Cost of treatment

- The newest drugs are very expensive
- Criticism of industry, but why companies charge so much for new drugs?
- Transfer of manufacturing and R&D to the cheaper countries (BRICS, 3rd world). This leads to cheaper drugs but also means loss of employment in industrialised countries (Roche – new manufacturing facilities in Shanghai, Rio de Janeiro; Takeda – manufacturing in all BRIC countries and beyond (Indonesia, Colombia, Mexico etc.)

The New York Times
25 April 2013

Doctors Denounce Cancer Drug Prices of $100,000 a Year

With the cost of some lifesaving cancer drugs exceeding $100,000 a year, more than 100 influential cancer specialists from around the world have taken the unusual step of banding together in hopes of persuading some leading pharmaceutical companies to bring prices down.

Prices for cancer drugs have been part of the debate over health care costs for several years — and recently led to a public protest from doctors at a major cancer center in New York. But the decision by so many specialists, from more than 15 countries on five continents, to join the effort is a sign that doctors, who are on the front lines of caring for patients, are now taking a more active role in resisting high prices. In this case, some of the specialists even include researchers with close ties to the pharmaceutical industry.

The doctors and researchers, who specialize in the potentially deadly blood cancer known as chronic myeloid leukemia, contend in a commentary published online by a medical journal Thursday that the prices of drugs used to treat that disease are astronomical, unsustainable and perhaps even immoral.

Correct choice of drugs

- Particularly important due to high cost and high risk associated with treatments
- Heterogeneity of cancers (various genetic alterations can lead to the same disease): genetic screening tests become mainstream
- Full sequencing of individual genomes is an ultimate solution

Cost of genome sequencing

Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcosts. Accessed [March 6th 2013].

Funding of research

- New ideas rarely come from industry.

  However:

- Implementation is usually done by industry
- Reason: huge (up to 90%) failure rate of new drugs

The Sydney Morning Herald

Deadliest cancers lose funding race

Date February 3, 2012

Julie Robotham

Lung and pancreatic cancers are receiving little funding ... Carole Renouf, chief executive of the National Breast Cancer Foundation.

CANCER research spending in Australia is fragmented and wasteful and has failed to tackle the deadliest forms of the disease, say representatives of charities and government funding bodies who want an overhaul of the $300 million sector.

Women's cancers including those of the breast, cervix and ovary were funded generously compared with the amount of death and disease they caused, said the chief executive of charity the National Breast Cancer Foundation, Carole Renouf.

But lung and pancreatic cancer, which have high death rates, received a relatively small fraction of overall cancer funding from government research agencies and independent organisations.

Lung cancer, which is responsible for about 20 per cent of Australian cancer deaths, receives only 1 per cent of research funding, an analysis by Cancer Australia found.

Pressure of Wall Street

- IRESSA: 20% drop in AstraZeneca share prices in 2005 after drug failure, followed by long bear market

- Lessons: a) tighter risk management needed;

b) money can be saved by exploiting more reliable leads

Market capitalization: US$ 42.38 bn

New leads: combinatorial chemistry or nature?

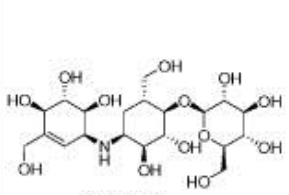
Lipinski's rule of five:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient log *P* not greater than 5

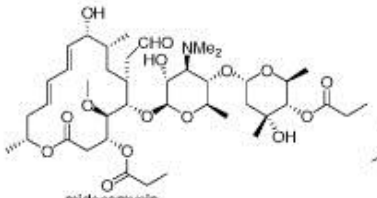
Imagination of nature seems to exceed ours by orders of magnitude

Problems:

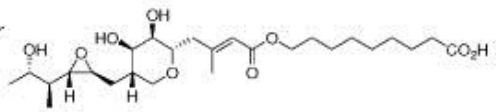
- Multiple active ingredients are common. Difficult to establish which one is important.
- Clinical trials problematic to arrange in standard conditions – hard to compare (Green tea: no drugs despite established effect)



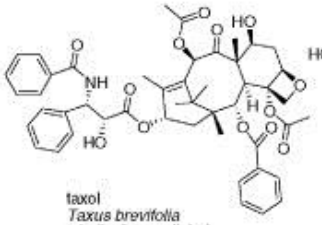
validamycin
Streptomyces hygroscopicus
α-glucosidase (intracellular)



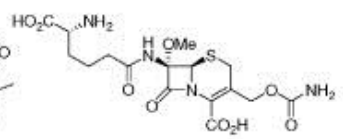
midecamycin
Streptomyces mycarofaciens
50S ribosome (intracellular)



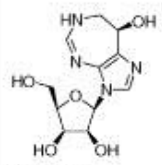
pseudomonic acid
Pseudomonas fluorescens
Ile t-RNA synthetase (intracellular)



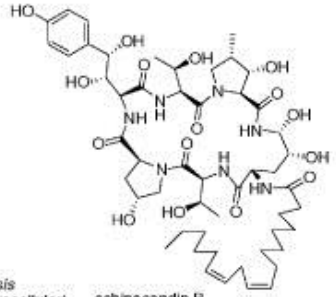
taxol
Taxus brevifolia
tubulin (intracellular)



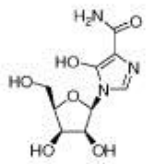
cephamycin C
Streptomyces clavuligerus
penicillin-binding proteins (cell wall)



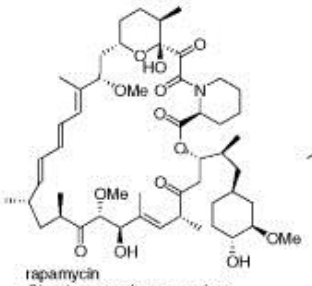
coformycin
Streptomyces kaniharaensis
adenosine deaminase (intracellular)



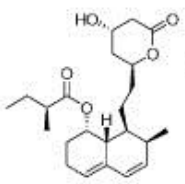
echinocandin B
Aspergillus nidulans
β-1,3-D-glucan synthase (cell wall)



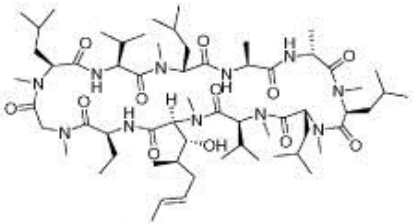
mizoribine
Eupenicillium brefeldianum
inosine monophosphate dehydrogenase (intracellular)



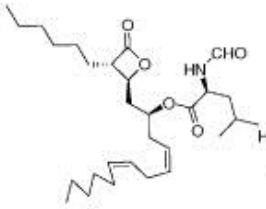
rapamycin
Streptomyces hygroscopicus
mammalian target of rapamycin (intracellular)



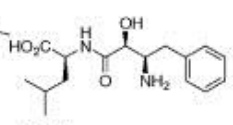
compactin
Penicillium citrinum
HMG CoA reductase (intracellular)



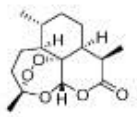
cyclosporine A
Tolypocladium inflatum
calcineurin (intracellular)



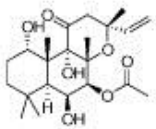
lipstatin
Streptomyces toxytricini
pancreatic lipase (extracellular)



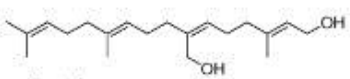
bestatin
Streptomyces olivoreticuli
aminopeptidase (intracellular)



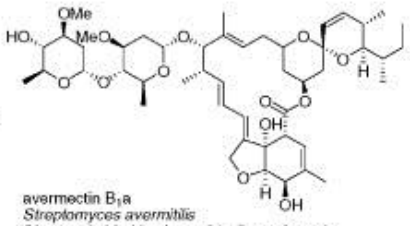
artemisinin
Artemisia annua
P. falciparum
oxidative damage (intracellular)



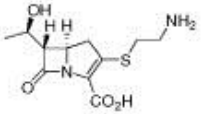
forskolin
Coleus forskohlii
adenylyl cyclase (cell membrane)



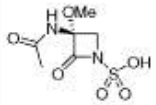
plaunotol
Croton subilyratus
H. pylori (cell membrane)



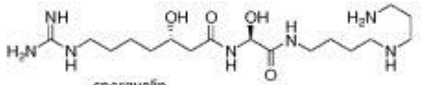
avermectin B_{1a}
Streptomyces avermitilis
Glu-gated chloride channel (cell membrane)



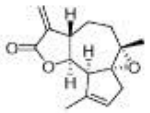
thienamycin
Streptomyces cattleya
penicillin binding proteins (cell wall)



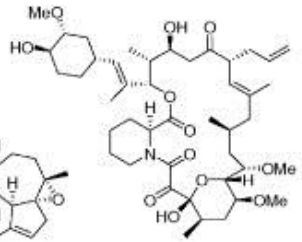
SQ26,180
Chromobacterium violaceum
penicillin binding proteins (cell wall)



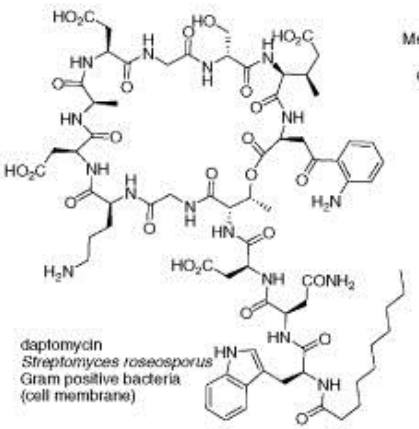
spergualin
Bacillus laterosporus
T-cell maturation (intracellular)



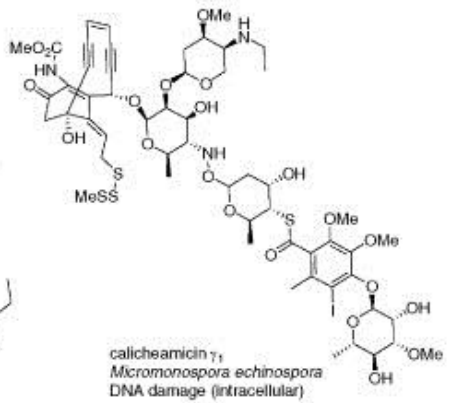
arglabin
Artemisia glutinosa
farnesyl transferase (cell membrane)



FK506
Streptomyces tsukubaensis
calcineurin (intracellular)



daptomycin
Streptomyces roseosporus
Gram positive bacteria (cell membrane)



calicheamicin γ_1
Micromonospora echinospora
DNA damage (intracellular)

The 'parallel universe' of successful natural product leads

NP	Formula	MW	log *P*	Hd	Ha	Rot	PSA	HA	St
Validamycin	$C_{20}H_{35}NO_{13}$	498	-5.2	12	14	7	253	34	14
Midecamycin	$C_{41}H_{67}NO_{15}$	814	2.1	3	16	14	206	57	9
Pseudomonic acid	$C_{26}H_{44}O_9$	501	2.5	4	9	17	146	35	8
Taxol	$C_{47}H_{51}NO_{14}$	854	3.0	4	14	14	221	62	11
Echinocandin B	$C_{52}H_{81}N_7O_{16}$	1060	1.8	14	16	20	368	75	15
Rapamycin	$C_{51}H_{79}NO_{13}$	914	4.3	3	13	6	195	65	15
Cyclosporine A	$C_{62}H_{111}N_{11}O_{12}$	1203	5.2	5	12	15	279	85	12
Lipstatin	$C_{29}H_{49}NO_5$	492	7.5	1	5	21	82	35	5
Avermectin B_{1a}	$C_{48}H_{72}O_{14}$	873	2.3	3	14	8	170	62	20
FK506	$C_{44}H_{69}NO_{12}$	804	3.3	3	12	7	178	57	14
Daptomycin	$C_{72}H_{101}N_{17}O_{26}$	1621	-3.7	22	29	35	702	115	13
Calicheamicin γ_1	$C_{55}H_{74}IN_3O_{21}S_4$	1368	3.2	8	23	24	308	84	19
Average	$C_{46}H_{70}N_4O_{14}$	917	2.2	7	15	16	259	64	13

NP, natural product; MW, molecular weight; log *P*, *C* log *P*; Hd, H-bond donors; Ha, H-bond acceptors; Rot, number of rotatable bonds; PSA, polar surface area; HA, heavy atom count of nonhydrogen atoms; St, stereogenic centers. Values generated by the PubChem database.

A Ganesan (2008) **The impact of natural products upon modern drug discovery** Curr Opin Chem Biol. 12(3):306-17

€9m EU-project on deep-sea organisms started

© Kirsti Helland - University of Tromsø, Norway

13.02.2013 - The collaborative project PharmaSea will bring European researchers to some of the deepest, coldest and hottest places on the planet. Scientists from the UK, Belgium, Norway, Spain, Ireland, Germany, Italy, Switzerland and Denmark will work together to collect and screen samples of mud and sediment from huge, previously untapped, oceanic trenches. The large-scale, four-year project is backed by more than €9.5 million of EU funding and brings together 24 partners from 13 countries from industry, academia and non-profit organisations.

Imagination of nature seems to exceed ours by orders of magnitude

Problems:

- Multiple active ingredients are common. Difficult to establish which one is important.
- Clinical trials problematic to arrange in standard conditions – results are hard to compare (Green tea: no drugs despite established effect)

Rare cancers

- No chances for industry to make profits
- Difficult to arrange proper clinical trials. Most treatments remain experimental
- Orphan cancers often have specific genetic alterations – possibility of finding a very specific target (CML: success story; specific genetic changes in Ewing sarcoma and lung mesothelioma)

Communication gap between science and patients

- Many patients don’t have full information about treatment options
- Many clinicians don’t know about new developments in their fields
- Many patients are unaware of the side effects and/or limited usefulness of anticancer drugs

Cancer. 2009 April 1; 115(7): 1424–1434. doi:10.1002/cncr.24186.

Colon Cancer Patient Information Seeking and the Adoption of Targeted Therapy for On-Label and Off-Label Indications

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[2] School of Medicine and Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania

[3] Center of Excellence in Cancer Communication Research, Annenberg School for Communication, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Background—Despite the rise in publicly available cancer information little is known about the association between patient information seeking and the adoption of cancer technologies. We investigated the relationship between patient information seeking and awareness about and receipt of novel targeted therapy (TT) for colon cancer among patients for whom therapy is FDA approved and for whom therapy is not FDA approved.

Methods—A retrospective population-based survey of 633 colon cancer patients identified through the Pennsylvania Cancer Registry. Outcome measures were self-reported awareness about and receipt of TT (Avastin™ and Erbitux™).

Results—After adjusting for sociodemographic characteristics, high levels of treatment information seeking were strongly associated with hearing about TT (odds ratio [OR] 2.83; 95% confidence interval [CI] 1.49-5.38) and receiving TT (OR 3.22; 95% CI, 1.36-7.62). These associations were present for patients with metastatic disease where use of TT is FDA approved and for patients with localized disease where use of TT is not FDA approved (p-value for interactions 0.29). Internet and newspaper/magazine use was associated with hearing about TT (OR 2.88; 95% CI 1.40-5.94; OR 3.44; 95% CI 1.34-8.84). Seeking information from non-treating doctors was associated with hearing about and receiving TT (OR 1.95; 95% CI, 1.03-3.68; OR 2.64; 95% CI, 1.16-5.97).

Conclusions

- Better drugs will be developed in the next few years, but no game changers so far

However:

- Even with existing methods of cancer treatment there is a lot of avenues and possibilities to improve clinical outcome

Thank you for your attention!

Additional information about the drugs under development – on my website (www.wlassoff.com)

Email: info@wlassoff.com