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Drug Discovery – Some Current Trends

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Drug discovery is hard

Rare diseases

‘All diseases are rare’

Alternative approaches; immunotherapy

Current biotech bubble

Formulation

Genetic Code, Initiation, & Eukaryotic Protein Synthesis

LMB, Cambridge 1967-70

Cytoplasmic Methionine Transfer RNAs from Eukaryotes

by
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Eukaryotic cells contain two species of methionine accepting tRNA. One of these (Met-tRNA$_{F^*}$) only incorporates methionine into N-terminal positions of polypeptid... whereas the other (Met-tRNA$_{M^*}$) donates methionine into inte... tRNA$_{F^*}^{Met}$ is an initiator tRNA...

TRANSFER RNA from bacteria contains two methionine accepting species tRNA$_F^{Met}$ and tRNA$_M^{Met}$. Methionine attached to tRNA$_F^{Met}$ can be enzymatically formylated to give formylmethionyl tRNA$_F$ (fMet-tRNA$_F$), while methionyl tRNA$_M$ (Met-tRNA$_M$) does not accept formyl groups[2]. fMet-tRNA$_F$ is the chain initiator on the 70S found in all prokaryotes and prokaryotic-type chloroplasts and mitochondria[3]. A ... the initiator tRNA is that ... donates methion... of newly syn...

properties su... and the sp... implies th... adapted ... The ... unkn... in th... gu...

(Reprinted from Nature, Vol. 225, No. 5228, pp. 184–187, January 10, 1970)

Translation of RNA from Encephalomyocarditis Virus in a Mammalian Cell-free System

THE role of formylmethionyl tRNA$_f$ (fMet-tRNA$_f$) in the initiation of protein biosynthesis in *Escherichia coli* is now reasonably well understood[1]. A similar mechanism involving fMet-tRNA$_f$ seems to be common to all 70S type ribosomal systems including those from bacteria, chloroplasts and mitochondria[2,3]. The corresponding process on 80S type ribosomes is, however, as yet unknown, but there is no evidence to suggest that fMet-tRNA$_f$ or any similar blocked aminoacyl-tRNA is involved[3]. A mammalian cell-free system which syn-

The size of Rou... active in cell-free

Tony Pawson*, Robert Harvey &...
Department of Molecular Virology, Imperial Czec...

Sedimentation analysis of mRNA from RSV-... cells suggests that Pr76, the precursor to the vir... protein, is synthesised on a mRNA of similar size to virion RNA, whereas a protein with molecular weight 70,000 tentatively identified as the non-glycosylated precursor to the viral glycoprotein, gp85, is synthesised on a smaller size class of mRNA.

ROUS sarcoma virus (RSV) contains a genomic virion 70S RNA which in denaturing conditions dissociates into two apparently identical 30–40S RNA subunits[1,2]. We and others have translated RSV virion 30–40S RNA in cell-free systems derived from mammalian cells[3–7]. The major in vitro product of RSV virion 30–40S RNA is a polyprotein similar, if not identical, to the 76,000 molecular weight precursor to the group-specific (gs) antigens, Pr76, which is found in RSV-infected cells[8]. Pr76 synthesised in vitro in response to RSV virion 30–40S RNA can be labelled with *N*-formyl-methionine derived from the initiator tRNA[9]. Since fMet can ...

...structural ... in a different amount and translated at a different efficiency, the viral proteins need not be synthesised in equimolar amounts. This model also suggests that virion 30–40S RNA has internal initiation sites and that they are inactive.

To examine the mechanism by which RNA tumour virus proteins are synthesised, we have isolated total poly(A)-containing cytoplasmic mRNA from RSV-infected chick cells. This mRNA has been fractionated on denaturing sucrose gradients, translated in mammalian cell-free systems derived from mouse ascites and L cells. Because infection by RNA tumour viruses does not shut off host-cell metabolism and viral mRNA constitutes only a small fraction of total mRNA activity, the viral proteins made *in vitro* were isolated by immunoprecipitation using various antisera raised against avian RNA tumour virus proteins.

Fractionation of infected cell mRNA

Poly(A)-containing cytoplasmic RNA was isolated from c/o chick embryo fibroblasts transformed with non-defect... Prague-C RNA, from uninfected chick cells, and fr...

Initiator Codons in Eukaryotes

by
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A uniqu... riboson... only i... GUG

THE cytoplasm of several eukaryotes contains two Methionine accepting tRNAs (tRNA$_{F^*}^{Met}$ and tRNA$_{M^*}^{Met}$)[1]. Methionine attached to tRNA$_{F^*}^{Met}$ can be formylated by *Escherichia coli* transformylase[1], while Met-tRNA$_{M^*}$ does not accept formyl groups. In an *E. coli* cell-free system eukaryotic fMet-tRNA$_{F^*}$ functions as an initiator with the same requirements and specificity as *E. coli* fMet-tRNA... donates methionine only into ... discrimination against the Met-tRNA... by the corresponding aminoacyl-tRNA bindi...

Function of Tumor Antigens and Identification of Nuclear Localisation - Mill Hill, London 1980-1984

Reprinted from Nature, Vol. 311, No. 5981, pp. 33-38, 6 September 1984
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Sequence requirements for nuclear location of simian virus 40 large-T antigen

Daniel Kalderon, William D. Richardson, Alexander F. Markham* & Alan E. Smith

Cell, Vol. 18, 915–924, December 1979. Copyright © 1979 by MIT

Protein Kinase Activity Associated with Polyoma Virus Middle T Antigen in Vitro

Alan E. Smith, Ros Smith, Bet
Mike Fried†
Translation, Nucleic Acid* and
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Imperial Cancer Research Fun
Lincoln's Inn Fields
London WC2, England.

Summary

A protein kinase activity can
noprecipitates of extracts fro
infected cells using antiseru
transformed cells (anti-T seru
detected in uninfected cells
serum. Using rat anti-T serum
the heavy chain of rat IgG

Cell, Vol. 39, 499–509, December 1984 (Part 2). Copyright © 1984 by MIT

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A Short Amino Acid Sequence Able to Specify Nuclear Location

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William D. Richardson, and Alan E. Smith
Biochemistry Division
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Mill Hill
London NW7 1AA, England

Summary

A short sequence of amino acids including Lys-128 is required for the normal nuclear accumulation of wild-type and deleted forms of SV40 large T antigen

below M_r 15,000 is not detectably retarded, a globular protein of M_r 67,000 (BSA) enters nuclei only very slowly, and a protein of M_r 450,000 (ferritin) is excluded (Paine et al., 1975). From such studies, the nuclear envelope has been proposed to behave as an array of cylindrical pores of internal diameter 7–11 nm (Paine et al., 1975; Peters, 1984). This model of the envelope corresponds reasonably well with the dimensions of discrete structures called nuclear pores, which have been purified from the nuclear envelope and analyzed by electron microscopy (Harris, 1981; Unwin and Milligan, 1982).

It appears therefore that in vivo many small proteins may

Reprinted from Nature, Vol. 303, No. 5916, pp. 435-439, 2 June 198
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Polyoma virus transforming protein associates with the product of the c-src cellular gene

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Molecular Basis of Cystic Fibrosis

Genzyme 1989-1995

Expression of cystic fibrosis transmembrane conductance regulator corrects defective chloride channel regulation in cystic fibrosis airway epithelial cells

Devra P. Rich, Matthew P. Anderson, Richard J. Gregory, Seng H. Cheng, Sucharita Paul, Douglas M. Jefferson, D. McCann, Katherine W. Klinger, Alan E. Smith & Michael J. Welsh

Howard Hughes Medical Institute, Departments of Internal Medicine, Iowa 52242, USA
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Demonstration That CFTR Is a Chloride Channel by Alteration of Its Anion Selectivity

Matthew P. Anderson, Richard J. Gregory, Simon Thompson, David W. Souza, Sucharita Paul, Richard C. Mulligan, Alan E. Smith, Michael J. Welsh

Expression of the cystic fibrosis transmembrane conductance regulator (CFTR) generates adenosine 3′,5′-monophosphate (cAMP)–regulated chloride channels, indicating that CFTR is either a chloride channel or a chloride channel regulator. To distinguish between these possibilities,

Cell, Vol. 63, 827–834, November 16, 1990, Copyright © 1990 by Cell Press

Defective Intracellular Transport and Processing of CFTR Is the Molecular Basis of Most Cystic Fibrosis

Seng H. Cheng, Richard J. Gregory, John Marshall, Sucharita Paul, David W. Souza, Gary A. White, Catherine R. O'Riordan, and Alan E. Smith
Genzyme Corporation
Framingham, Massachusetts 01701

Cell, Vol. 73, 1251–1254, July 2, 1993, Copyright © 1993 by Cell Press

Molecular Mechanisms of CFTR Chloride Channel Dysfunction in Cystic Fibrosis

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Cystic Fibrosis

The genetic defects underlying this lethal disease have now been shown to eliminate or hobble a critical channel through which a constituent of salt enters and leaves cells

by Michael J. Welsh and Alan E. Smith

Drug Discovery is hard

We still have much to learn about human biology and disease

Takes a long time; costs a great deal; most things fail

For last 30+ years, as more money has been spent in pharma R&D, less drugs have been approved

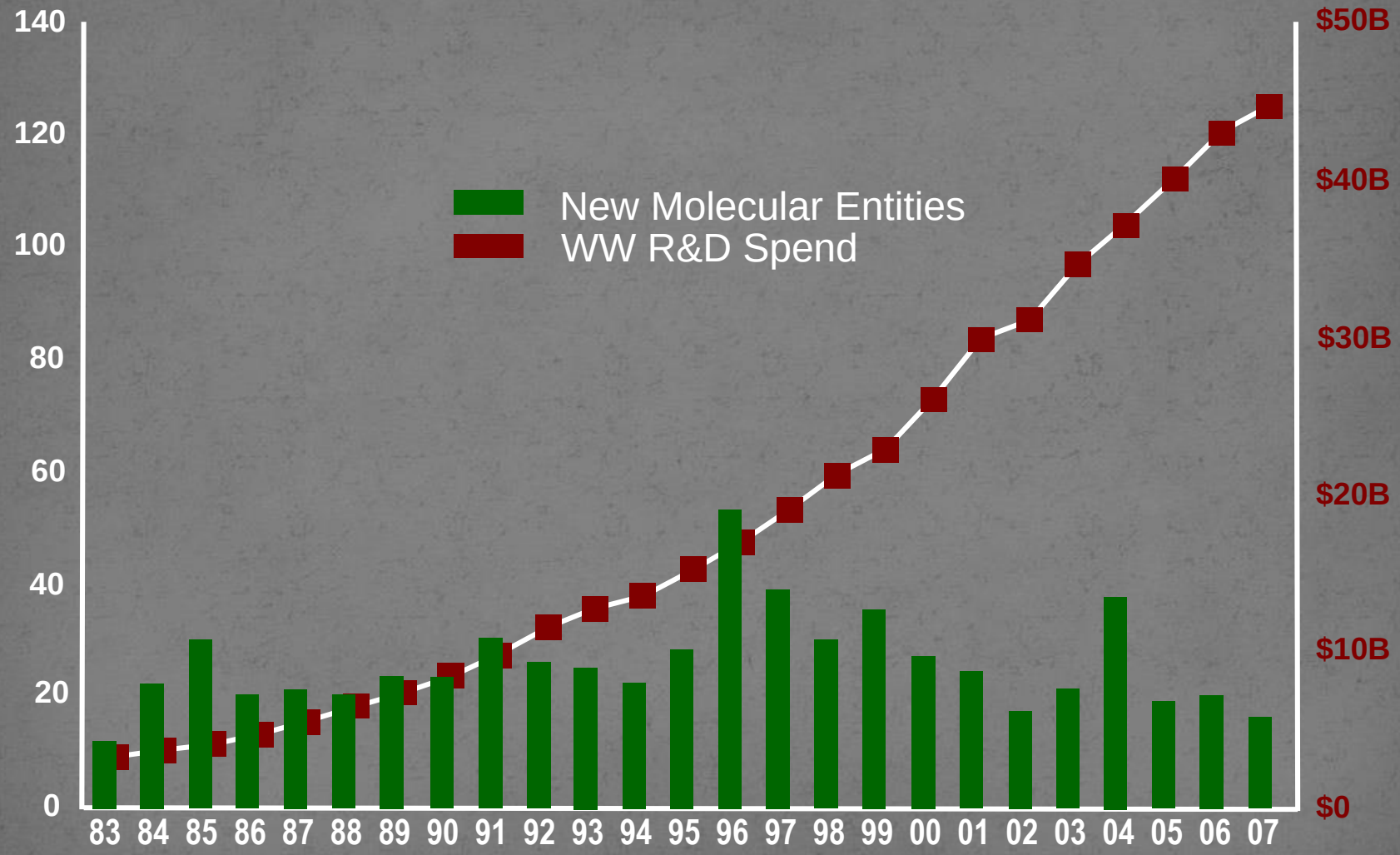
Most pharma have concluded this is a poor investment and that they are unable to discover drugs in house

Current model is to outsource much early research

Pharma become Development and Sales & Marketing

Does outsourcing discovery work any better?

For 25 years Biopharma R&D spending grew steadily …
but paradoxically no correlation with more novel drugs approved



Drug Discovery is hard

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Does outsourcing discovery work any better?

Opportunity for start ups

Innovation greater in early start ups?

Costs in start ups much less; Infrastructure minimized

New ideas pushed rapidly to proof of concept in early human trials

Most of these also fail

Successes valued hugely

Overall do the finances work better in this model?

Biotech Madness – a recent example

Alexion acquires Synageva for $8.4 bn - Spring 2015

Only drug: Kanuma (sebelipase alfa), a treatment for the ultra rare lysosomal acid lipase deficiency (LAL-D)

Recently approved EU, presently under FDA's priority review program,

Alexion made its name with Soliris, another ultra rare disease treatment ($500,000 a year)

This valuation is crazy

Rare Orphan diseases

Considered to be more likely to succeed

Molecular mechanisms established, in humans

Therapy often replacement, rather than interventional

Few patients mean that price is very high

Value created by high efficacy in most patients

Pioneered by Genzyme, now universal

As more developed, total cost becoming prohibitive?
(1% of drugs cost 30% of total spending)

All diseases are rare

As molecular mechanisms of disease unraveled many major diseases sub-categorised

Each sub category becomes ‘rare’

Example, breast cancer; at least a dozen mechanisms

Rare disease approach yields higher success rates

Price for each drug necessarily will be very high

Total drug costs will become unsustainable

New needs and opportunities

A general approach to cancer is very attractive

Immune involvement in control of cancer known for 100+ years – Colley's adjuvent

Earlier approaches unsuccessful – tumours developed resistance to immune attack

New approaches that circumvent immune counter attack (eg check point inhibitors) extremely promising

Early approvals in hand, multiple major programs

A very promising 'novel' approach to cancer

New financial models

Early research and late development relatively easy to finance

Translational work, ‘valley of death’ more difficult

New models constantly tested

US Cystic Fibrosis Foundation recently sold Vertex royalty stream for $3bn +

Foundations, patient organisations & hospitals will copy

A new funding source with strong vested interest

Biotech Bubble

For several years biotech start up valuations have been extremely high

More recently in EU & UK

Biotech stocks outperforming for 5 years in US

Although turnover is high, the industry is thriving

This will not last

Opportunism and luck are key components
go for it while you can!

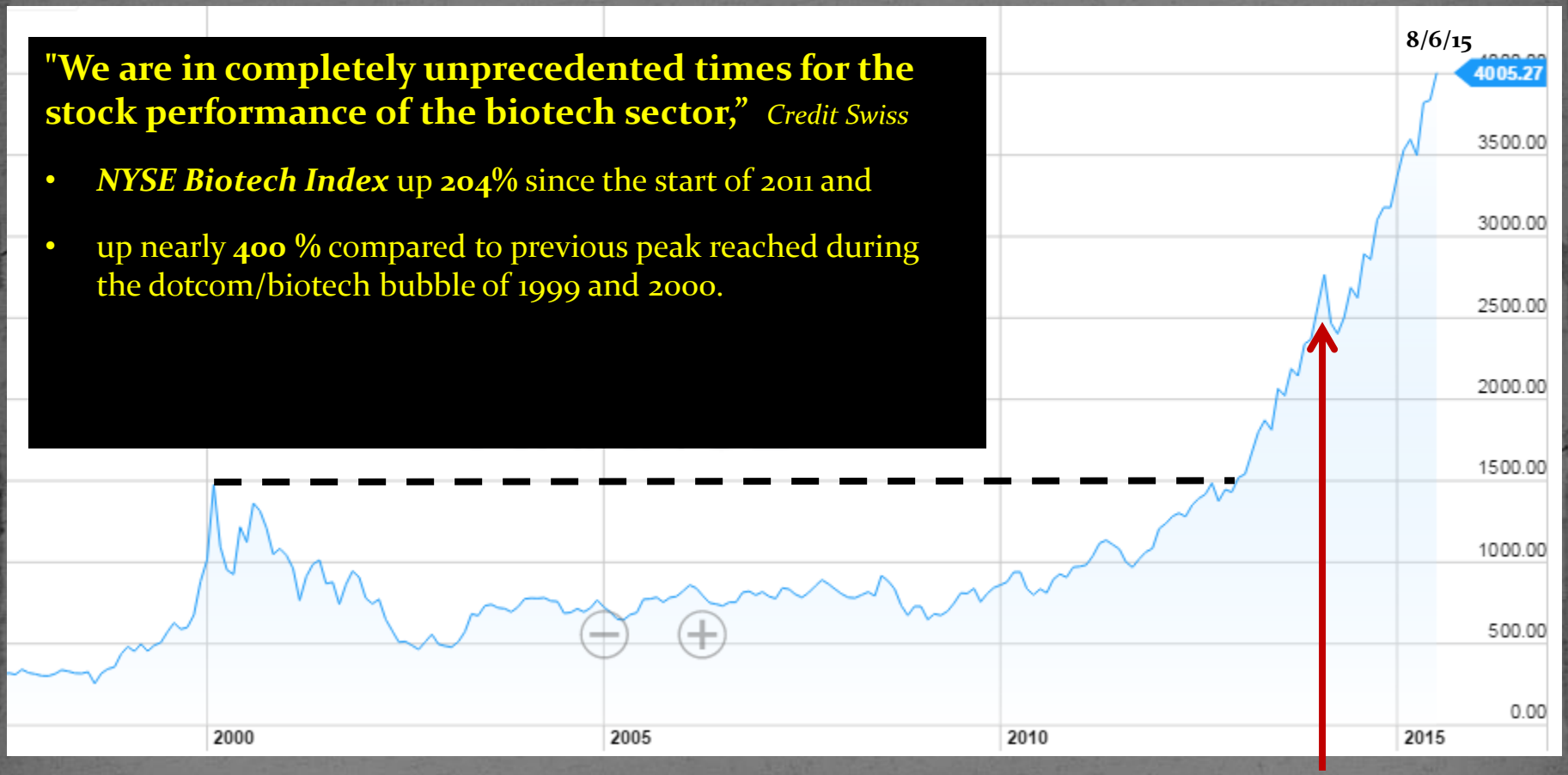
Q1 2013 … Biotech Stocks Pass 2000 Peak Levels …

NBI = NASDAQ Biotech Stock Index

… and have kept on going!

"We are in completely unprecedented times for the stock performance of the biotech sector," *Credit Swiss*

- ***NYSE Biotech Index*** up **204%** since the start of 2011 and
- up nearly **400 %** compared to previous peak reached during the dotcom/biotech bubble of 1999 and 2000.



Federal Reserve Chair Janet Yellen:

… Some valuation metrics are substantially stretched, particularly Biotech

Formulation

New drugs are relatively few

Add maximum value to existing proven drugs

Formulation can be key; particularly in biologics

Insulin has been a successful drug almost 100 years

Total sales insulin today higher than ever

Formulation of existing drugs offers a low risk opportunity to add value for patients and investors

Thank you

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