The Effect of Serendipity in Drug Discovery and Development

Emily Hargrave-Thomas, Bo Yu and Jóhannes Reynisson

School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142 (e-mail: *j.reynisson@auckland.ac.nz*)

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Introduction

It is well known that serendipity has played a pivotal role in the discovery of many drugs used today.[1-3] Indeed, two major classes of anticancer drugs were discovered with the aid of serendipity, i.e., Barnett Rosenberg's discovery of cisplatin and the breakthrough observation by Lieutenant Colonel Stewart F. Alexander that the chemical warfare agent nitrogen mustard depleted white blood cell numbers; aiding in the development of alkylation agents.[1-2] The question that therefore emerges is how important serendipity really is in drug discovery and development. The aim of this investigation is to compile a list of all marketed drugs and their derivatives used in the clinic today in which discovery was in some way based on or aided by a serendipitous event. The numbers obtained will be compared to the total number of marketed drugs, resulting in a quantitative measure of the impact of serendipity in the discovery of pharmaceuticals.

Methodology

Three books were analysed: *Laughing Gas, Viagra, and Lipitor*: *The Human Stories Behind the Drugs We Use*, [1] *Happy Accidents: Serendipity in Modern Medical Breakthroughs* [2] and *Drug Discovery, a History*.[3]In addition, one scientific paper was examined that contained a list of drugs discovered by the aid of serendipity.[4] These resources were studied and the stories containing serendipitous events were recorded. The nature of the serendipitous findings were categorised as ***laboratory based*** or ***clinical***. The drugs identified were reviewed in DrugBank [5-7] and only those that were approved, small molecule, and in clinical use were compiled. Furthermore, drugs with similar chemical structures and with the same notation (i.e., used to treat the same condition) as the parent drug were considered to be their derivatives, as identified by substructure and Tanimoto similarity searching in DrugBank.[5-7]

Serendipity in drug discovery and development

Serendipity refers to chance discoveries that have been exploited with sagacity.[3] This requires both a chance event and the mental ability to understand the occurrence and realize its potential. In this work, only stories that fit both requirements for serendipity were recorded. The serendipitous events were divided in to two categories; ***laboratory based*** and ***clinical***. A classic example of the former is Barnett Rosenberg's discovery of cisplatin, and an example of the latter is dimenhydrinate (Dramamine), which was developed as an antihistamine, but is now sold as a travel sickness medication owing to a chance observation/realisation by one of the participants in the clinical trials. The division of the drugs into these two categories is not always obvious but we believe that it helps in the analysis of the results. In his book *Serendipity* Royston M. Roberts coined the term "pseudoserendipity" to describe accidental discoveries of ways to achieve an end sought, in contrast to the meaning of 'true' serendipity, which describes accidental discoveries of things not sought. [8] Certainly, all of the drugs discovered in the clinic can be described as pseudoserendipitous according to this definition, as can many of the ones found in the laboratory.

To calculate the proportion of drugs with a serendipitous background, the total number of small molecule drugs on the market (FDA approved) is taken to be 1437, according to DrugBank.[5-7] Overington *et al.*[9] reported 1204 small molecule drugs in clinical use, which is a somewhat smaller number. It can be explained by noting that about 20 new drugs are released on the marked annually and the use of some is discontinued. Also, some drugs are allowed in Europe and elsewhere but not in the USA, which makes it difficult to define a precise number of drugs in worldwide clinical use.

In this analysis 84 drugs were identified to have serendipitous events aiding their discovery, which is 5.8% of all drugs currently in use. 31 drugs (2.2%) were found in the laboratory and 116 derivatives (8.1%) of these drugs were found, as shown in Table 1. 53 pharmaceuticals (3.7%) were discovered in clinical settings and 147 derivatives (10.2%) of those were identified (see Table 2). Therefore, in total there are 347 drugs currently on the market, in which discovery was aided by a serendipitous event, representing a staggering 24.1% of all drugs currently on the market. A graphical representation of the results is given in Fig. 1.

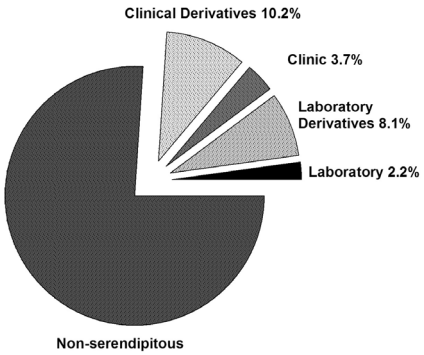

Fig. 1. The distribution of the serendipity types (***laboratory based*** and ***clinical***) and their chemical derivatives in clinical use (100% = 1437).

Serendipity in anticancer drug discovery and development

According to DrugBank[5-7] there are 88 anticancer drugs in clinical use today. Of the drugs identified with a ser-

Table 1 List of drugs discovered with the aid of serendipity in the laboratory, the number of identified derivatives and their therapeutic application.

Laboratory Drugs	Reference	Number of Derivatives	Application
Acetanilide	a(p.438) ,b	1	Antipyretic
Acetohexamide	a(p.393),b, c(p.184)	8	Diabetes II
Captopril	a(p.281), c (p.88)	8	Cardiovascular
Cisplatin	a(p.63), b, c(p.10), d(p.136)	2	Cancer
Diethylstilbestrol	a (p.196), b	1	Hormonal
Digoxin	a(p.39), c(p.84)	4	Cardiovascular
Ergotamine	a (p.341), c(p.159), d(p.296)	6	Cardiovascular
Ephedrine	a (p.100)	9	CNS
Griseofulvin	a (p.297), b	0	Antifungal
Heparin	a (p.269), b, d(p.234)	4	Cardiovascular
Isoniazid	a (p.396), b	0	Antibiotic
Lidocaine	a (p.434)	6	CNS
Lithium	a (p.62), b, c(p.140), d(p.261)	0	CNS
Marinol	a(p.111)	1	CNS
Mechlorethamine	a(p.440), b, c (p.8), d(p.122)	5	Cancer
Mecillinam	a (p.323)	1	Antibiotic
Methotrexate	a (p.249), c(p.18)	1	Cancer
Nalidixic Acid	a (p.394), c (p.69)	8	Antibiotic
Nitroglycerine	a (p.433), b, c (p.80)	2	Cardiovascular
Penicillin	a (p.289), b, c(p.54), d(p.59)	21	Antibiotic
Pentamidine	a (p.277)	0	Antiprotozoal
Physostigmine	a (p.96)	0	Ocular
Quinine	a (p.77)	1	Antiprotozoal
Sorafenib	d (p.163)	0	Cancer
Streptomycin	c (p.63), d (p.86)	7	Antibiotic
Sulfanilamide	a (p.384), c (p.50), d(p.54)	13	Antibiotic
Valproic acid	a (p.444),b	1	CNS
Vinblastine	a (p.102), c(p.12), d(p.133)	3	Cancer
Dicoumarol	a (p.111), b, d (p.236)	0	Cardiovascular
Warfarin	a (p.137), b, d (p.237)	3	Cardiovascular
Zinc Sulfate	a (p.62)	0	Wilson's disease

a=Ref.[3]; b=Ref. [4]; c=Ref.[1]; d=Ref.[2]; CNS = Central Nervous System.

endipitous origin, 13 are used to treat cancer and 18 are their chemical derivatives. This means that 35.2% of all anticancer drugs in clinical use had serendipity involvement of some kind. The statistical distribution is shown in Fig. 2. This is a larger portion of serendipitous effect than for pharmaceuticals in general, described in the previous section.

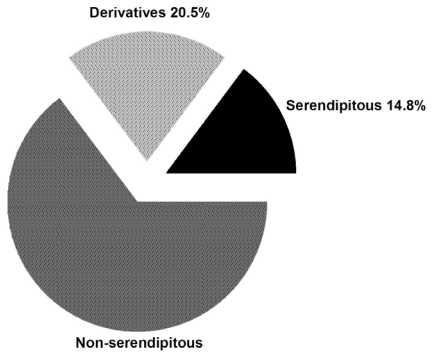

Fig. 2. The statistical distribution of anticancer drugs discovered with the aid of serendipity and their chemical derivatives in clinical use (100% = 88).

Of the primary serendipitous events anticancer drugs represent 15.5% (13/84), i.e., a sizeable portion. However, relatively few derivatives were found for anticancer drugs (6.8% of the derivatives). This highlights the difficulty in developing effective anticancer drugs.

The effect of serendipity in different therapeutic areas

When the primary serendipitous events are investigated it is clear that antibiotic, anticancer, cardiovascular and CNS drugs are the most common therapeutic application, with ~10 events for each (see Tables 1 and 2). Other therapeutic fields such as antiprotozoal and antifungal are also reported. Also, less common treatments for such conditions as gout and alcoholism occur. A high frequency of CNS discoveries is seen in the clinical settings in Table 2, i.e., 17 out of the total of 53. This reflects the difficulty in developing drugs that need to pass the Blood-Brain-Barrier[10] and the dearth of biochemical assays modelling the diseases of the mind and pain.

Discussion

Recently a new concept of Known Drug Space (KDS) has been developed to help drug designers to navigate chemical space based on the analysis of drugs in clinical use.[11-13] It is known that 10% of KDS are unaltered natural products and 29% are their derivatives (semi-synthetics).[14] Natural products are typically identified in screening pro-

Table 2 List of drugs found to be beneficial for other conditions than for which they were developed (clinical), the number of identified derivatives and their therapeutic notation.

Clinical Drugs	Reference	Number of Derivatives	Notation
Aminoglutethimide	a (p.367),b	0	Cancer
Alprostadil	a (p.186)	4	Cardiovascular
Amphetamine	a (p.130), b, c (p.160)	10	CNS
Aspirin	a (p.360), c(p.222), d (p.237)	0	Cardiovascular/Cancer
Auranofin	a (p.60) , d (p.137)	0	Anti-rheumatic
Carbamazepine	a (p.415)	1	CNS
Celecoxib	d (p.149)	0	Cancer
Chlordiazepoxide	a (p.411), b, c (p.135), d (p.282)	20	CNS
Chlorothiazide	a (p.391), b, c (p.86)	11	Diuretic
Clofibrate	a (p.274)	1	Cardiovascular
Dactinomycin	a (p.311)	0	Cancer
Diisopropyl fluorophosphate	a (p.435)	0	Ocular
Diltiazem	a (p.412)	0	Cardiovascular
Dimenhydrinate	a (p.405), b, d (p.2)	0	CNS
Diphenhydramine	a (p.405)	2	CNS
Diphenoxylate	a (p.124), b	1	Antidiarrheal
Dipyridamole	a (p.134)	0	Cardiovascular
Disulfiram	b, c (p.130), d (p.285)	0	Alcoholism treatment
Doxorubicin	a (p.313)	5	Cancer
Etomidate	a (p.335), b	0	CNS
Finasteride	d (p.311)	1	Baldness
Guanethidine	a (p.277), b	2	Cardiovascular
Haloperidol	a (p.123), b, c (p.154)	1	CNS
Imatinib	c (p.39)	0	Cancer
Imipramine	a (p.413) b, c (p.145), d (p.278)	10	CNS
Iproniazid	a (p.397), b, c (p.142), d(p.275)	1	CNS
Linezolid	c (p.144)	0	Antibiotic
LSD	a (p.350), b, c(p.159), d (p.288)	5	CNS
Meprobamate	b, d(p.271)	1	CNS
Mercaptopurine	a (p.253), c (p.19)	2	Immunosuppressive
Metronidazole	a (p.334)	1	Antiprotozoal
Mifepristone	a (p.203), b	0	Hormonal
Minoxidil	d (p.311)	0	Cardiovascular
Mycophenolic acid	a (p.289)	1	Immunosuppressive
Naloxone	a (p.120)	1	CNS
Norethindrone	a (p.200), b, c (p.118)	11	Hormonal
Pethidine	a (p.122), b	1	CNS
Phenobarbital	a (p.369)	6	CNS
Prednisone	a (p.208), b	6	Anti-inflammatory
Probenecid	d (p.78)	0	Gout
Procarbazine	a (p.397)	0	CNS
Promethazine	a(p.408), c (p.152), d (p.267)	20	Antihistamine
Quinacrine	a (p.382)	4	Antiprotozoal
Reserpine	a (p.102), c (p.138), d (p.274)	2	CNS
Salicyclic acid	a (p.358)	4	Anti-rheumatic
Sildenafil	a (p.136), c (p.111), d (p.222)	2	Erectile dysfunction
Sirolimus	a (p.306)	1	Immunosuppressive
Tamoxifen	a (p.199), b, c (p.23), d (p.139)	1	Cancer
Terfenadine	a (p.406)	1	Antihistamine
Thalidomide	c (p.20), d (p.151)	1	Cancer
Tolazoline	a (p.371)	0	Cardiovascular
Trimethadione	a (p.439)	1	CNS
Zidovudine	a (p.260), d (p.122)	5	Antiviral

a=Ref.[3]; b=Ref. [4]; c=Ref.[1]; d=Ref.[2]; CNS = Central Nervous System. LSD = Lysergische Säure Diäthylamid (lysergic acid diethylamide).

grams of soil bacteria and other biological sources, i.e., they are found but *not* designed. With this fact and the results presented in this paper it can be stated that KDS is to a large extent populated by chance rather than design. Using the drugs thus identified for analysis of their physicochemical properties reveals the right parameters for drug candidates and therefore allows for a designing element in drug discovery projects.

Serendipity in drug discovery has not been investigated to a great extent, but some papers were found in the literature. Opinions expressed vary greatly, which is not surprising

owing to the ambiguous nature of this phenomenon. For instance, Jeste *et al.* downplayed the importance of serendipity, arguing that few if any drug discoveries in their field of psychiatry were truly serendipitous.[15] Conversely, Lombardino and Lowe stated that "the role of serendipity, chemical intuition and creativity in thoughtfully selecting a chemical target to synthesize in order to discover the best-quality drug has not diminished" irrespective of the introduction of new technologies.[16] Furthermore, Klein strongly believed that a loss of chance observations and unexpected clinical benefits are due to recent changes in the process of drug discovery.[17] He criticises cost-control measures which remove a creative environment in hospitals that fosters serendipity.[17] Finally, Kubinyi suggested that researchers should not be manipulated by short-term business cycles: drug discoveries require good science, enlightened management, and freedom for researchers to act, challenge dogma and take risks.[4]

This investigation provides a limited scope of serendipitous drug discovery since only four sources were analysed. It is certain that not all serendipitous events are recorded; researchers may choose not to report them in favour of standard scientific methods of inquiry. It can therefore be argued that the impact of serendipity may be even larger than found in this investigation.

According to the results presented here ~24% of all drugs currently on the market were discovered with the aid of serendipity and, thus, may never have been discovered without the curiosity, observation, and sagacity of the researchers. This serves to highlight the unpredictability in drug research and the necessity to allow for and encourage freedom in research directions and ensure continuation of and promote the intellectual freedom of the scientists involved. Also a sound education in science is indispensable and the encouragement of critical thinking of our students is vital. The practice of teaching to the test where there are only *right* or *wrong* answers should be strongly discouraged (for further discussion see Lenox[18]).

Understanding the serendipity phenomenon is crucial so we can start to manipulate it to our advantage. We believe that quantifying serendipity's impact facilitates our understanding of it. Finally, Pasteur's comment on serendipity[19] certainly still holds true: "Dans les champs de l'observation, le hasard ne favorise que les esprits préparés" ["In the field of observation, chance favours only the prepared mind"]

Conclusions

This study found that 24% of all pharmaceuticals currently on the market were affected in a positive way during their development by serendipity, with CNS active drugs being very prominent for discoveries made in the clinic. Furthermore, 35.2% of all the anticancer drugs now in clinical use were discovered with the aid of serendipity. This leads to the conclusion that drug discovery is based on good science and intuition, critical thinking, sagacity and open-mindedness play crucial roles.

References

1. Li, J.J. *Laughing Gas, Viagra, and Lipitor The Human Stories Behind the Drugs We Use*. Oxford, Oxford University Press, 2006.
2. Meyers, M.A. *Happy Accidents: Serendipity in Modern Medical Breakthroughs*. New York, Arcade Publishing, 2007.
3. Sneader, W. *Drug Discovery, a History*. Chichester, John Wiley & Sons Ltd., 2005.
4. Kubinyi, H. *J. Rec. Signal Trans.* **1999**, *19*, 15-39.
5. Wishart, D.S.; Knox, C.; Guo, A.C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M. *Nucleic Acids Res.* **2008**, *36*, D901-D906.
6. Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. *Nucleic Acids Res.* **2006**, *34*, D668-D672.
7. Knox, C.; Law, V.; Jewison, T.; Liu, P.; Ly, S.; Frolkis, A.; Pon, A.; Banco, K.; Mak, C.; Neveu, V.; Djoumbou, Y.; Eisner, R.; Guo, A.C.; Wishart, D.S. *Nucleic Acids Res.* **2011**, *39*, D1035-D1041.
8. Roberts, R.M. *Serendipity Accidental Discoveries in Science*. Wiley Science Editions: New York 1989.
9. Overington, J.P.; Al-Lazikani, B.; Hopkins, A.L. *Nature Rev. Drug. Dis.* **2006**, *5*, 993-996.
10. King, A. *Chemistry World* **2011**, *June*, 36-39.
11. Ioakimidis, L.; Thoukydidis, L.; Naeem, S.; Mirza, A.; Reynisson, J. *QSAR Comb. Sci.* **2008**, *27*, 445-456.
12. Axerio-Cilies, P.; Castañeda, I.P.; Mirza, A.; Reynisson J. *Eur. J. Med. Chem.* **2009**, *44*, 1128-1134.
13. Mirza, A.; Desai, R.; Reynisson, J. *Eur. J. Med. Chem.* **2009**, *44*, 5006-5011.
14. Bade, R.; Chan, H.F.; Reynisson, J. *Eur. J. Med. Chem.* **2010**, *45*, 5646-5652.
15. Jeste, D.; Gillin, J.; Wyatt, R. *Archives of General Psychiatry* **1979**, *36*, 1173-1178.
16. Lombardino, J.; Lowe, J. *Nat. Rev. Drug Dis.* **2004**, *3*, 853-862.
17. Klein, D. *Journal of the American Medical Association* **2008**, *299*, 1063-1065.
18. Lenox, R.S. *J. Chem. Edu.* **1985**, *62*, 282-285.
19. Pasteur, L, Lecture, Université de Lille, 7 December 1854.