2015

Creation of an Annotated Library on FDA Approved Nanomedicines

Marley R. Hodson
Virginia Commonwealth University, hodsonmr@mymail.vcu.edu

Tanin Izadi
Virginia Commonwealth University, izadit2@mymail.vcu.edu

Nastassja Lewinski Ph.D
Virginia Commonwealth University, nalewinski@vcu.edu

Bridget T. McInnes Ph.D
Virginia Commonwealth University

VIRGINIA COMMONWEALTH UNIVERSITY

Creation of an Annotated Library on FDA Approved Nanomedicines

Tanin Izadi[1], Marley Hodson[1], Bridget T. McInnes, Ph.D.[2], Nastassja Lewinski, Ph.D.[1]

[1]Department of Chemical & Life Science Engineering [2]Department of Computer Science

Abstract

Nanomedicine is a type of nanotechnology used in the medical field to limit the dosage amount and target drug delivery to specific cells. Nanomedicines that are approved and used tend to be extremely successful; however despite over a decade of research, only a limited number of nanomedicines have advanced for clinical use. A possible reason for the numerous nanomedicine failures is lack of easily accessible information and research on previous nanomedicines. In this project, we have compiled nanomedicine labeling information from the Drugs@FDA website. We have extracted phrases/sentences from labels relating to keywords on nanomaterial properties and drug profile characteristics. In the future, we plan to incorporate discontinued nanomedicines, nanomedicines on the market, and nanomedicines in different clinical trial phases. By compiling the descriptions and contents of a set of specific nanomedicines, a machine learning program could be developed to comb through literature and automatically identify similar nanomedicine related entities. Our research works to provide an easier and quicker method to obtain specific information on approved nanomedicines.

Introduction

We are used to information being readily accessible. When it comes to the subject of nanomedicine that is no longer the case. The innovative world of nanomedicine hasn't evolved to its full advancing potential. The application of nanotechnology for medical purposes has the potential to greatly improve our world.

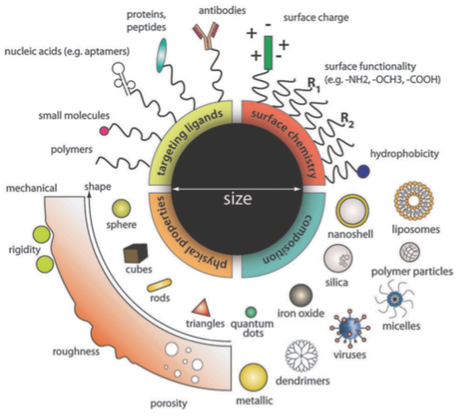

Figure 1. Different types of nanoparticles and ways they can be modified and developed [Image source: Ref. 1]

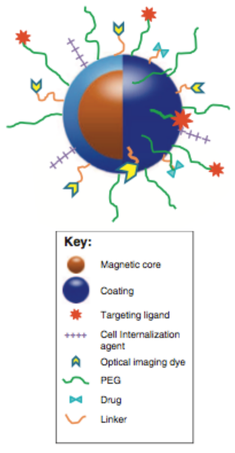

Figure 2. Illustration of a magnetic nanoparticle's "core-shell" structure. This example has a iron oxide core, which is common among magnetic nanoparticles. [Image source: Ref. 2]

Methods

Our initial database was based off of the work by Schutz et al. [3]. Figure 3 shows our Excel spreadsheet and consists of data collected from this paper. The Drugs@FDA website has been our primary source for retrieving nanomedicine labeling information. We extracted relevant data from the label information, which consisted of entities in the form of a phrase/sentence relating to nanomaterial properties and drug profile characteristics. These entities specifically included the trade name, phase, platform, surface coating, nanoparticle, max concentration, time to max concentration, generic/other name, company, indication, clearance, volume of distribution, active ingredient, size, route of administration, dose, dose form, plasma half life, and elimination half life. After the data was extracted, the sentences containing this data were placed into a separate Excel spreadsheet as shown in Figure 4. Figure 3 contains the entire database that was updated and filled with information received from the labeling documents during this project. The data was then analyzed to reveal any potential trends.

	Phase	Platform	Nanopartic	Surface Co	Trade Nam	Generic/Oth	Company	Indication	Active Ingr	Size (nm)	Route of ac	Dose		t1/2 (plasm	t1/2 (elimin	FDA appro	EU approv
2	Approved	Nanoparticle	TiO2		Anthelios 20		Loreal USA	sunscreen	avobenzone, ecamsule, (		Dermal					10/4/2002	
3	Approved	Nanoparticle	TiO2		Anthelios 40	Helioblock S	Loreal USA	sunscreen	avobenzone, ecamsule, (		Dermal					3/30/2004	
4	Approved	Nanoparticle	CaP		Elestrin		Jaz Pharm	menopause	estradiol		Dermal (transdermal)		54 8-75.2 hr			12/14/2002	
5	Approved	Micelle	soybean oil,	NR	Estrasorb	Estradiol top	Novavax, Gr	vasomotor s	estradiol hemihydrate		Dermal (transdermal)		57.6 hr			10/8/1999	
6	Approved	Virosome	spherical ve	NR	Epaxal		Berna Biote	hepatitis A v	immunopote	150	IM					not found	
7	Approved	Polymer-pro	asparaginas	PEG	Oncaspar	Oncospar, p	Enzon Pharr	Chemothera	pegaspargase	NR	IM or IV	2500 IU/m2	5.8 d (IM), 7	5.8 d		1/1/1990	
8	Approved	Virosome			Inflexal V		Berna Biote	influenza vaccine			IM or subcutaneous injection						
9	Approved	Polymer-apt	siRNA anti-\	PEG	Macugen		Eyetech Inc,	neovascular	pegaptanib sodium		intravitreal injection		10+/-4 hr			12/16/2000	1/30/2002
10	Approved	Nanoparticle	albumin	NR	Abraxane		Abraxis Bio	metastatic b	paclitaxel (bi	130	IV		27 hr			1/6/2001	1/10/2004
11	Approved	Polymer-pro	fab fragmen	PEG	Cimzia	Certolizuma	Nektar, UCE	Crohn's dise	humanized anti-TNF-alph		IV		14 d			4/21/2004	9/30/2005
12	Approved	Polymer-pro	interferon-al	PEG	PEGIntron		Enzon, Sche	hepatitis C	peginterferon alpha-2B		IV					1/18/1997	5/24/1996
13	Approved	Liposome	lipid	NR	AmBisome	Amphoterici	Astellas Pha	antifungal	amphotericin ~45-80		IV		24 hr	15 d		8/10/1993	
14	Approved	Liposome	lipid	NR	DaunoXome	Daunorubici	Diatos, Gile	antineoplast	daunorubicin-citrate		IV					4/7/1992	
15	Approved	Liposome	lipid	NR	Depodur	Depofoam	Pacira Phar	pain relief	morphine sulfate		IV					5/17/2000	
16	Approved	Liposome	lipid	NR	Mepact	L-MTP-PE	IDM Pharma	osteosarcor	mifamurtide		IV					NR	3/5/2005
17	Approved	Liposome	lipid	NR	Myocet		Sopherion T	antineoplast	doxorubicin	150	IV		2-3 d				7/12/1996
18	Approved	Liposome	lipid	NR	Visudyne	Verteporfin I	Novartis	photodynam	verteporfin		IV					4/20/1996	7/26/1996
19	Approved	Liposome	lipid	PEG	Doxil	Caelyx (EU)	Ortho Biotec	antineoplast	doxorubicin	105	IV		2-3 d			11/16/1991	6/20/1992
20	Approved	Liposome	lipid		Abelcet	Amphoterici	Sigma-Tau I	antifungal	amphotericin B		IV					11/19/1991	
21	Approved	Liposome	lipid		Amphotec	Amphoterici	Three Rivers	antifungal	amphotericii ~115		IV					11/21/1992	
22	Approved	Liposome	lipid		Diprivan		App Pharma	anesthetic	propofol		IV					10/1/1985	
23	Approved	Polymer-pro	monometho	PEG	Adagen	pegademas	Sigma-Tau I	enzyme repl	pegademase bovine		IV					3/20/1986	
24	Approved	Micelle	NR	NR	Taxol	cremophor,	Corden Pha	antineoplast	paclitaxel		IV					12/28/1988	
25	Approved	Micelle	poly(D,L-lac	PEG	Genexol-PM		Samyang Cc	antineoplast	paclitaxel	20-60	IV						

Figure 3. Screenshot of entire updated database.

1	**Phase** Initial U.S. Approval: 2002
2	**Platform** The antibody moiety of Zevalin is ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antig
3	**Nanopar** Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the mono
4	**Surface Coating**
5	**Trade Na** Zevalin is indicated for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NH
6	**Generic/(** Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the mono
7	**Compan** Zevalin® is a registered trademark of Spectrum Pharmaceuticals, Inc. and its subsidiaries.
8	**Indicatio** Zevalin is indicated for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NH
9	**Active In** Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the mono
10	**Size (nm)**
11	**Route of** Day 1: Administer rituximab 250 mg/m^2 intravenous. Day 7, 8, or 9: Administer rituximab 250 mg/m^2 intravenous infusion
12	**Dosage F** Each single-use vial includes 3.2 mg of ibritumomab tiuxetan in 2 mL of 0.9% Sodium Chloride.
13	**Dose** A clearly-labeled kit is required for preparation of Yttrium-90 (Y-90) Zevalin. Follow the detailed instructions for the prepar
14	**t1/2 (plas** Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days).
15	**Clearance**
16	**Volume of Distribution**
17	**Max Con** Severe cytopenias which may require stem cell support have occurred at doses higher than the recommended maximum tc
18	**Time of Max Concentration**
19	**t1/2 (elimination)**
20	**FDA app** Initial U.S. Approval: 2002
21	**U.S. Pate** Protected by U.S. Patent Nos. 5,736,137, 5,776,456, 5,843,439, 6,207,858, 6,399,061, 6,682,734, 6,994,840, 7,229,620, 7,3

Figure 4. Screenshot of our sentence extraction excel spreadsheet for the drug Zevalin.

Results/Discussion

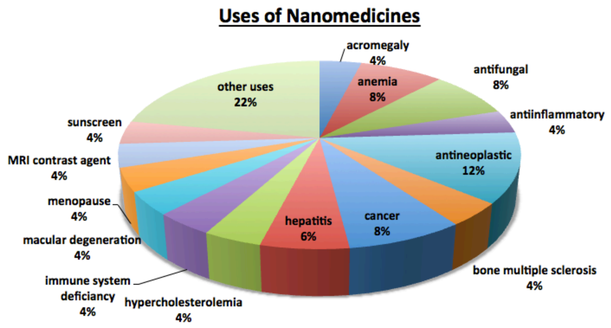

Figure 5. Prevalence of the different uses of FDA approved nanomedicines. Antineoplastics was the most common.

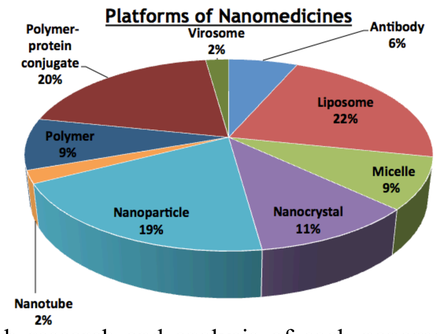

Figure 6. Prevalence of the different platforms each nanomedicine contained. Liposomes were the top platform used followed by Nanoparticles

After our thorough research and analysis of each nanomedicine, we were able to group and categorize the drugs based on their platforms and indications. When categorizing these characteristics we found different trends and correlations. There were seven total nanomedicines that had the indication of antineoplastic agents (medicines that target cancerous cells). Out of the seven antineoplastic nanomedicines, six had the platform of either a liposome or micelle. While liposomes and micelles share many similar qualities, the structure remains as the predominant difference. Micelles have a membrane monolayer, while liposomes have a bilayer, signifying the liposomes are generally larger in size. We conclude from this trend that encapsulating the drug in a liposomes and micelles is a more successful drug delivery method compared to attaching the drug to the surface of the particles. With many new nanomedicines in the pipeline, this trend can easily change in the future.

Conclusion

As we continue our research, we plan to work with Dr. McInnes's research team to develop a system that automatically extracts nanomedicine information. With the sentences we have collected and categorized, the system will be able to search for entities within the label information pdfs. With this entity extraction program, we will be able to promptly gather the relevant nanomedicine information. The shortened period for research allows for a clearer and quicker alternative in viewing the relationships between the different types of nanomedicines. Once the automation program is created, the current difficulties in retrieving background research on nanomaterials will dramatically decrease. This program will be able to extract entities from pdf files that the user inputs. A separate program that automatically searches for nanomedicine pdfs is also under development.

Acknowledgements

We would like to thank Lynn Secondo and Mahmoud Moustafa for providing us key information and guiding us throughout this project.

Works Cited

[1] Chou L, Ming K., Chan* W. "Strategies for the intracellular delivery of nanoparticles" *Chem. Soc. Rev.*, 2011, 40, 233–245.
[2]Cole A., Yang V., David A., "Cancer theranostics: the rise of targeted magnetic nanoparticles" *Trends in Nanotechnology*(2011) 29(7),
[3] Schutz C, Juillerat-Jeanneret L, Mueller H, Lynch I, Riediker M. "Therapeutic nanoparticles in clinics and under clinical evaluation." *Nanomedicine* (2013) **8**(3), 1–19.