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Raising financing through strategic timing

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We provide further detail on the global nanobiotechnology sample from which our exemplar was drawn, on our methodology for developing a proxy for patent value, and on the North American de novo nanobiotechnology firms which provide context. In section S1, we describe the selection and classification of our global nanobiotechnology sample. In section S2, we argue that the value of a patent to a de novo nanobiotechnology venture lies in the combination of the patent's broad, blocking and relevant nature. We then define and support our criteria for broad, blocking and relevant patents. Finally, in section S3, we present data on the founding, patenting and success of our entire sample of North American de novo nanobiotechnology drug delivery firms.

S1. Global Nanobiotechnology Firm Sample

With the goal of observing the emergence of the global nanobiotechnology industry in an earlier study[1], we created three distinct samples (cohorts) for longitudinal analysis. These cohorts consist of firms with both biotechnology and nanotechnology capabilities in 2005, 2008 and 2011. We used the DMS IndustryAnalyser, DMS NewsAnalyser, and Medtrack databases to identify a pool of biotechnology firms targeting human health which potentially held nanotechnology capabilities, whether integrated or in separate research divisions.

Next, we verified the existence and timing of development of both sets of capabilities through web searches, press releases, publications, and US patents. Nanotechnology patents were identified using keywords adapted from recent studies[2,3] and biotechnology patents were identified using standard guidelines based on patent sub-classes[4]. Using the patent filing date from the first of the selected patents (assigned to the company or its relevant subsidiaries) and comparing with the founding year of the firm, we were able to classify firms as *de novo* if the difference between the founding year and year of acquisition of nanotechnology capability was 3 years or less. Firms with more than 3 years difference between founding and year of acquisition of nanotechnology capabilities were identified as *de alio* or incumbent firms. In cases where firms had not yet had patents assigned to them, press releases, company documents, scientific publications and industry reports were used to identify the initial year of development of nanotechnology capabilities. These additional data sources allowed us to retrospectively supplement each cohort if these sources indicated such capability development prior to their date of entry in the three databases used. We are more specific to nanotechnology by limiting our inclusion criteria to firms with nanoscale capabilities defined as less than 300 nm, as opposed to the 1000 nm criteria utilised by the earlier studies[5,6]. Using data from company documents, industry reports and the DMS and Medtrack databases, we also classify the biotechnology firms as belonging to specific sub-sectors which help us to examine the evolution of nanobiotechnology at the level of the sub-sector.

S2. Broad, Blocking, Relevant Patents

Firms rely on patents to protect their inventions from imitation by describing in their claims, the exact product, component or process improvement that they have invented. Patents are more valuable to new ventures and to their investors when they are broad, blocking and relevant. A broad patent is one which enables a wide range of applications (more value creation): filing a broad patent requires forethought of how widely a patent can be applied in the future. A blocking patent enables a venture to appropriate that value, as competitors have difficulty inventing around such a patent. A relevant patent is one which is deemed promising and useful, (for example, because it meets an unmet market need, has a large potential social impact, and/or is in an emerging area of scientific discovery) stimulating significant follow on activity both by the firm and by others[7,8]. Broad, blocking, relevant patents can be particularly useful for science-based ventures, as they generally have little other than patents to show as an outcome of their research and development activity in the initial years after venture formation, and these become a key asset for attracting investors and alliance partners.

The broader the patent claims in a particular patent, the more difficult it is for competitors to invent around through alternative mechanisms, fields of use or extension of parameters. Broad patent claims can therefore limit competitors from pursuing a specific scientific path by preventing them from using a particular molecule / particle or a particular mechanism, leading to such patents being described as "blocking" patents. So defined, the breadth and blocking nature of patents are inextricably linked. Competitors have limited options when faced with broad, blocking patents. They can search for alternative methods to try and invent around such patents, or more

commonly in the biotechnology domain, in-license the rights to use and improve these technologies. In-licensing and further development can then lead to higher forward patent citations for these patents, despite their blocking nature.

Following extant literature[9], we argue that the presence of the word "comprising" in the first 500 characters of the patent claims is a strong indicator of broad, blocking patents.

"The term *comprising* is what is known as an open term. In effect, comprising is a shorthand way of saying "including the following elements but not excluding others." For example, a claim to a combination comprising A + B covers a combination having A + B + C. In general, a patent attorney drafts claims containing a minimum number of elements that will function in a combination and uses the open term comprising in order to cover the invention as ***broadly*** [emphasis ours] as possible under the patent." (Radack, 1995)

The claim structure of a patent is indicative of the importance of claims with the most important claims or *independent claims* being at the written at the beginning. Thus by limiting our search for the word "comprising" to the first 500 characters of the patent claims, we assess if the most important claims in a patent are broad and blocking or not.

The existing literature has used several indicators to assess patent breadth. Commonly used indicators of patent breadth such as the number of claims[10] or the number of 4-digit IPC/ US patent sub-classes[11] may not adequately capture the breadth of an invention covered by a patent in the biomedical sector. While it is commonly argued that patents with a larger number of claims may be broader, it is also possible that a larger number of claims may indicate that the patent breadth/ scope has been specified in very minute detail, which would indicate that the patent is not necessarily broad or blocking.

A broad biomedical patent (validated by IP lawyers), might target multiple disease indications but be classified within a single 4 digit IPC class such as C12N. This calls into question the idea that the breadth of a patent could be assessed by the number of 4-digit IPC sub-classes. There is some evidence to support this view: "narrower" patents with a smaller number of 4-digit IPC subclasses may be more litigated[10] (litigation being a measure of the value of patent rights), than patents which are broader as measured by a larger number of 4-digit IPC subclasses.

The value of patents has also been proxied by forward patent citations[10]. These forward patent citations are an indicator of relevance and could be from self-citations or from citations by collaborators, licensees or others. Multiple forward citations, particularly within the first few years of patent issue, are indicative of the rapid uptake of the invention. They may also indicate the potential lifetime citations and patent value as early citations could be an important predictor of sustained R&D efforts in future.

We argue that the value of a patent to a science-based venture, and to their prospective investors, is in the *combination* of the broad, blocking and relevant nature of the patent. We infer this broad, blocking, relevant nature of a patent through both the presence of the word "comprising" in the first 500 characters of the claims *and* the rapid accumulation of forward patent citations with the first 10 years from patent grant. In doing so we respond to recent calls to develop and use combinations of procedural and text based indicators of patent value[12]. This metric is particularly appropriate for the long timeframes and competitive landscape of the biomedical sector.

It could be argued that a blocking patent will not have any forward citations, as successful blocking would preclude other inventions from building on the protected IP. However, a patent can be both blocking (to competitors) and the basis of further inventions building on the claims[7]. In this instance, forward citations are an indicator of the cumulative investment of time and finances by the firm and a network of collaborators, signalling the value of the technology. The threshold of 10 forward citations in 10 years is appropriately high as biotechnology and pharmaceutical patents receive an average of 2 patent citations in the first 4 years[13]. Additionally, the distribution of citations per patent being extremely skewed[14] indicates that most patents have little value.

We agree that the comprising language may be used by several applicants, and this approach on its own may not provide enough specificity, but argue that when combined with patent forward citation data, it provides a more robust, selective and accurate measure of the value of patents to biomedical ventures. We therefore argue that the *qualities* of a patent which leads it to be cited multiple times early in its life are its *broad, blocking* and *relevant* nature.

S3. Assessing North American Nanobiotechnology De Novo Drug Delivery Firms

Drawing on the global nanobiotechnology sample, we further analyze the 39 North American de novo drug delivery firms (Table S1). We gather data on all the US patents assigned to these firms as of 2nd June 2016. We carefully checked for the presence of the word "comprising" within the first 500 characters of the patent claims. After gathering founding years for each of the firms in the sample, we calculated the number of granted patents which were filed for within the first five

years since founding. This metric "strategically timed patents", demonstrates the rapid development and protection of technology by the firm. This was followed by calculating the forward patent citations for each patent assigned to these 39 firms. Based on these forward citations, we examined if more than 10 forward patent citations were received within 10 years of the issue date of the patent, or if more than 5 forward patent citations were received within 5 years of the issue date of the patent (to avoid a truncation bias for more recently founded firms). Using this data, we were able to identify the number of broad, blocking and relevant patents as those having the word "comprising" and 5 year cites more than 5 or 10 year cites more than 10. We also identified those firms which achieved an initial public offering (IPO) and the date on which it was achieved.

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Table S1: Analyzing Strategic Timing of North American Nanobiotechnology De Novo Drug Delivery Firms

Firm Name	Country	Region	Firm Founding Year	IPO Date	Strategically timed patents*	Total US Patents granted#	Broad Blocking Relevant Patents@
Aradigm Corp.	USA	California	1991	01-May-96	28	120	77
Aphios Corp.	USA	Massachusetts	1993		6	17	8
Supratek Pharma	CAN	Quebec	1994		12	30	12
BioSante Pharma	USA	Illinois	1996		2	12	0
Lyotropic Therapeutics	USA	Virginia	1999		3	18	4
Dermazone Solutions	USA	Florida	2001		0	3	0
Nanocopoeia	USA	Minnesota	2001		0	4	0
Mersana Therapeutics	USA	Massachusetts	2002		0	10	1
Aegis Therapeutics	USA	California	2003		2	20	1
Asklepios BioPharma	USA	North Carolina	2003		2	3	0
Azaya Therapeutics	USA	Texas	2003		1	1	1
Arrowhead Research Corp.	USA	California	2003		0	17	0
ChimeraCore	USA	California	2004		2	2	0
NeuroSystec Corp.	USA	California	2004		2	3	0
Nanotrope	USA	California	2004		1	1	0
TransGenex Nanobiotech	USA	Florida	2004		0	1	0
AcelRx Pharma	USA	California	2005	11-Feb-11	9	18	8
NanoCor Therapeutics	USA	North Carolina	2005		1	1	0
GMD Bio Advance	USA	California	2005		0	0	0
Intellect Neurosciences	USA	New York	2005		0	6	0

Leonardo Biosystems	USA	Texas	2005		0	0	0
BIND Therapeutics	USA	Massachusetts	2006	25-Sep-13	12	36	26
Cerulean Pharma	USA	Massachusetts	2006	15-Apr-14	1	19	3
iCeutica	USA	Pennsylvania	2006		1	13	0
Lux Biosciences	USA	New Jersey	2006		1	2	0
NanoValent Pharma	USA	Montana	2006		0	0	0
Targeted Cell Therapies	USA	Massachusetts	2006		0	0	0
Arrogene Nanotech	USA	California	2007		1	3	0
Nanomed Devices	USA	New York	2007		1	2	1
Aura Biosciences Inc	USA	Massachusetts	2007		0	0	0
Medical Nanotech	USA	Texas	2007		0	0	0
NanoMedical Systems	USA	Texas	2007		0	0	0
NanoPacific Holdings	USA	California	2007		0	0	0
NanoVector	USA	North Carolina	2007		0	0	0
Savara	USA	Texas	2007		0	0	0
AeonClad Biomedical	USA	Texas	2007		0	0	0
Ensysce Biosciences	USA	Texas	2008		1	1	0
Pharmasonic Technologies	USA	California	2008		0	0	0
DLVR Therapeutics	CAN	Ontario	2011		0	0	0

* Number of granted US patents filed within five years from firm founding.

Total granted US patents assigned to the firm until 2 June 2016.

@ Number of Granted US Patents with "comprising" in the first 500 characters of the patent claims, and 5 or more forward patent citations within five years of patent issue date, or 10 or more forward patent citations within 10 years of patent issue date.