Editorial

Why China is currently underperforming in medical innovation and what China can do about it?—Part II

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Our AME survey-002 results indicated that, compared with Euro-American countries, China is underperforming in medical innovation (1-3) (Supplementary 1). To further explore this point, a metric literature analysis was carried out. The method was similar to the recent Zhang *et al.*'s paper (4). Ten reputable medical journals were included as the indicator for analysis, i.e., (I) *Circulation Research*; (II) *Blood*; (III) *Leukemia*; (IV) *Stem Cells*; (V) *Haematologica*; (VI) *Thrombosis and Haemostasis*; (VII) *Journal of Thrombosis and Haemostasis*; (VIII) *Arteriosclerosis, Thrombosis, and Vascular Biology*; (IX) *Journal of Cerebral Blood Flow and Metabolism;* and (X) *British Journal of Haematology*. All papers, including reviews and case reports, published during the periods of 1990-2014 by four countries, China (Mainland), Japan, Germany, and Switzerland, were retrieved, and where the corresponding author was affiliated with the above geographic regions were considered to be research output by the respective regions. As compared with English-speaking countries, all these four countries do not have a large proportion of guest researchers. The annual research and development (R&D) expenditure of each region was also retrieved (5); and the results are shown in *Figure 1*.

While the increase over the year 1990-1997 periods represents an overall global tendency to publish more papers (same patter was seen for UK and France), *Figure 1* also demonstrates the difficulty to decipher the relationship between R&D expenditure, literature output, and the perceived strength of the healthcare industry of respective countries. It is not easy to understand how the national policies, incentives and linguistic issues played a role. The R&D expenditure of China had a steep increase, Germany and Japan had a relative stable R&D investment with only small incremental increase, while Switzerland had only a fraction of R&D expenditure compared to the other three. China's publication improved very notably over the years; currently standing at the similar level of Switzerland in paper number. Though I knew Switzerland has good reputation of doing high quality of science and documents published by Swiss scientists tend to rank the top on citation per article (6-8), Switzerland is also the home for pharmaceutical giants like *Novartis* and *Hoffmann-La Roche*, it still caught me by surprise with I generated this graph. I congratulate Swiss scientists that they apparently did an excellent job. We also need to take notice that there will likely be a 'lagging effect'; with the investment associated the performance of Chinese medical scientists will further improve in the future. On the other hand, these data do agree with the common notion that a nation's scientific performance is not necessarily related to its general population size, such as Miller (9): "*good science can only be done by a small minority of each country's population*"; Kanazawa (7): "*Science is…inherently elitist*"; Murray [(3), p.310]: "*Great human accomplishment has not come about just because the world accumulated enough people*".

I generated the annual growth rate of Gross Domestic Product (GDP) in purchasing power parity (PPP), R&D expenditure (in PPP), and healthcare expenditure (in % PPP GDP) of China Mainland, the result is shown in *Figure 2*. The result suggests the increase in R&D investment is associated with the increase of China's GDP instead of some stimulus measures.

The countries with top 20 R&D spending in year 2012 are shown in *Figure 3*. While China ranked the second in overall

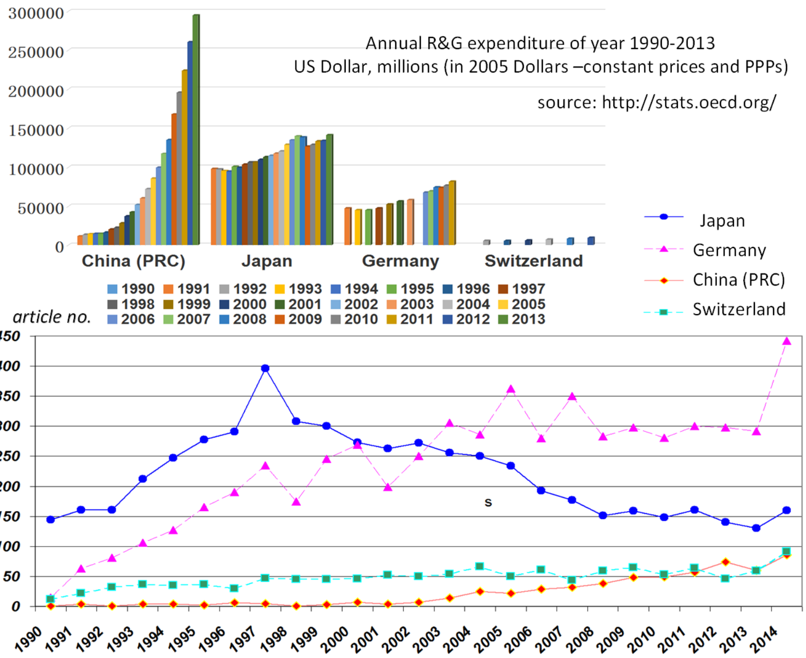

Figure 1 Year 1990-2013 annual R&D expenditure (in PPP) and publication output in ten reference medical journals by China, Japan, Germany, and Switzerland. There has been a steady decline since its peak in 1997 for Japanese scientists to publish in the 10 reference medical journal. However, there is no perception that the Japanese research capability deteriorated since 1997. Available online: http://stats.oecd.org/. R&D, research and development; PPP purchasing power parity.

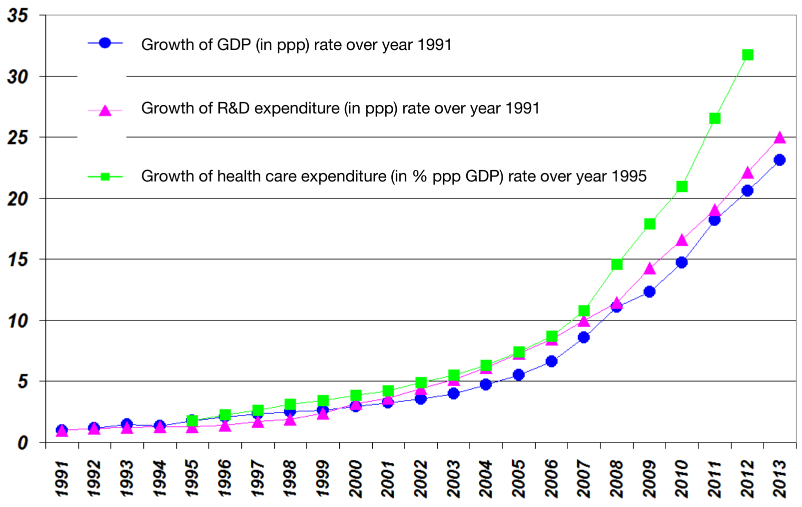

Figure 2 Year annual growth rate of GDP (in PPP), R&D expenditure (in PPP), and healthcare expenditure (in % PPP GDP) of China Mainland. Available online: http://data.worldbank.org/. GDP, Gross Domestic Product; PPP, purchasing power parity; R&D, research and development.

R&D spending, the contribution from Chinese corporations was very small, being 3.2% of the world total in 2013. Therefore the R&D spending of China has been largely driven by the government, which might partially explain for the low efficiency of R&D in China. However, according to one study (10), the top 10 R&D spenders in 2013 were not the 10 most innovative companies. No correlation was found between how much companies spent on R&D

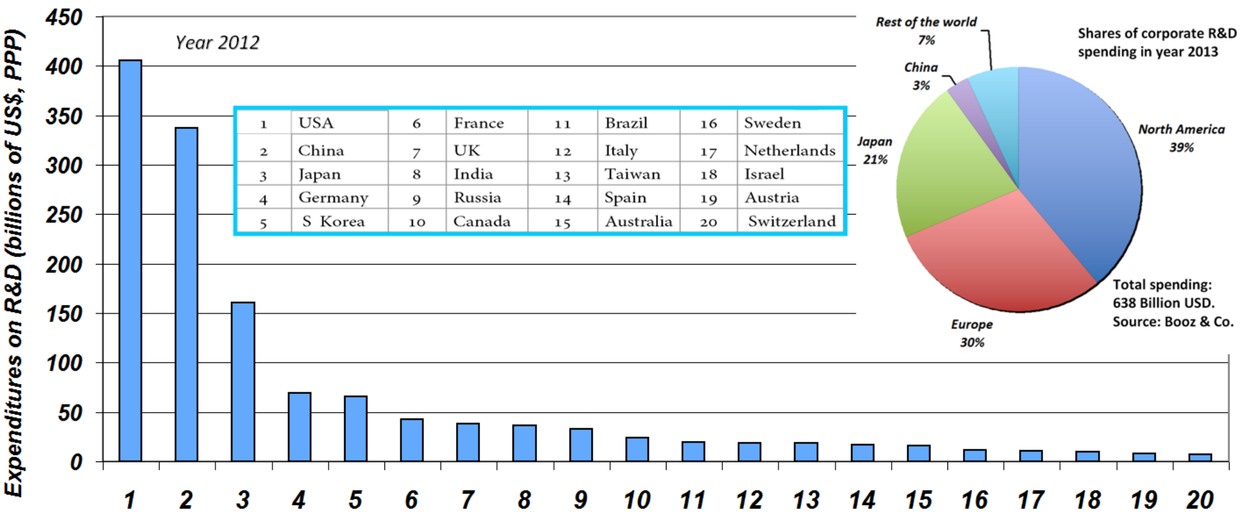

Figure 3 The top 20 countries with R&D spending in year 2012. The corporation R&D spending is shown in the insert. Available online: http://data.worldbank.org/; http://stats.oecd.org/. R&D, research and development.

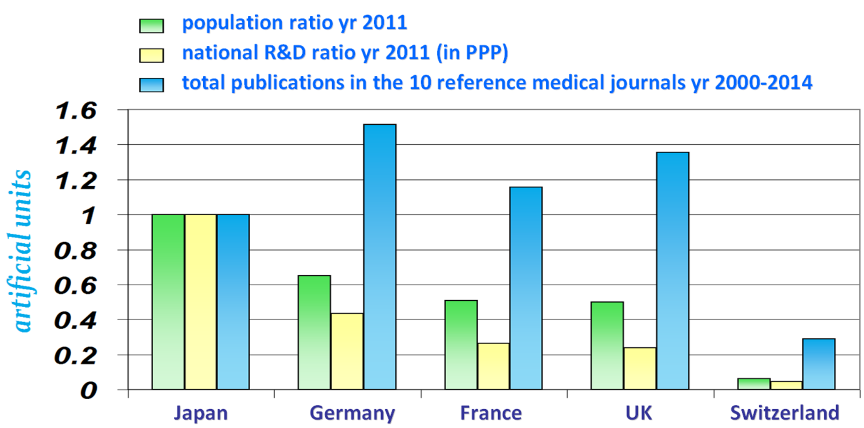

Figure 4 Comparison of Japan, Germany, France, UK and Switzerland in population size, annual R&D expenditure, and total publications in the 10 reference medical journals (presented in relative ratios). The values for Japan were adjusted to be one. Of note Japan has the combined population of France and UK; Japan's R&D spending was four times of that of UK or France, and more than twice than that of Germany. Available online: http://data.worldbank.org/; http://stats.oecd.org/. R&D, research and development.

and how well they performed over the long term (10). According to Steven Veldhoen at *Booz* (now strategy&, http://www.strategyand.pwc.com/), "*when it comes to innovation, how you spend is much more important than how much you spend*". *Figure 4* shows the comparison of Japan, Germany, France, UK and Switzerland in population size, annual R&D expenditure, and total publications in the 10 reference medical journals.

Historically China had a relatively weak track record in doing sciences (11) (*Figures S1,S2*). Using a statistical data base Dong *et al*. (11) concluded that the European area has been active in various scientific activities since 500 BC, and its scientific and technological achievements have always been outperforming China, and this is also reflected by the ancient architectural monuments scattered in the Eurasian Land. One significant obstacle for China is her geographical and linguistic isolation from the rest of the world, which is partially reflected in *Figure S1*, and also evidenced by our AME survey-001 which showed poor English literacy among many medical doctors (12). On the other hand, the annual *Eurovision* song contest with the creativity, the energy, and the diversity demonstrated by the participants is one testimony of the shared vibrant and continuous innovations among Eurolands countries (and also Israel and some Central Asia countries with geographical closeness to Europe). The overall poor English skill of Chinese people probably has a fundamental impact. Even educated Chinese are often disconnected with the outside world, leading to a cultural isolation, so that there is virtually no groundbreaking theories in humanities and arts, as well as in science, came out of China during the last century. The Soviet education system had been targeted as the scapegoat of underachievement in China sine *Xinhai* Revolution. However, USSR/Russia produced many Nobel Prize winners, Fields Prize winners, and many World Chess champions. While all Nobel Prize winners are certainly very clever, we also admit that some of them were the lucky ones, being at the right time at the right place [(3), p.149] . In areas which demands high level abstract thinking while does not require sophisticated instruments and team collaboration such as mathematics and chess (as measured by Fields Award, Turing Award and Chess championship), in last century China mainland's performance also paled (13-15). While our neighbor to the west India in her native land produced Chandrasekhara Venkata Raman [1888-1970] with Nobel Prize for Physics in 1930, Amartya Kumar Sen [1933-] with Nobel Prize in Economic Sciences in 1998, and Viswanathan Anand [1969-] with World Chess championship in year 2007-2013.

However, probably we should not be too concerned about our performance in hard science and innovation (16). We have good generic pharmaceutical companies. Yes we have to pay for novel drugs, but we do not pay for their expensive and risky R&D as well. One century after the *Xinhai* Revolution, we still do not drive in science and technology innovation; we just started to learn to participate in the world scene. But…and but, one century after Japan tried to challenge the supremacy of European imperial powers [Russo-Japanese War 1904-1905, Battle of Khalkhin Gol (Nomonhan Incident) 1939, Pacific War 1941-1945], even Japan still does not drive science yet, Japan is only participating (2,3,17). None of Internet, Microsoft, Apple, Google, originated from Japan. However, Japan does provide yet another type model for other countries to admire. Despite the *Lost Decade* in the 1990s and the Japanese real estate price bubble, the South Hyogo (Kobe) earthquake in 1995, and the Tohoku earthquake in 2011, Japan remains a resilient and orderly country, with low crime rate and high social security. Japan's healthcare is regarded as one of the most efficient in the world (18). Japan is the world's third largest donor of official development assistance after the US and France, donating US$9.48 billion in 2009 (19). The Japanese population enjoys the highest life expectancy of any country in the world (20).

After written all these, I realized that I could not offer better solutions for the difficulties China is facing in life science innovation. I can only repeat the following common senses: (I) for civil research, Chinese scientists should not only collaborate with international scientists, more importantly, Chinese research and international research should be integrated (some examples listed in Appendix 1), thus to partially offset China's lack of experience in research management; (II) in current atmosphere it is difficult to balance the research output quantity and quality; then the better way is the old and tested model that makes fresh faculty members to compete for output in metric terms while let the tenured staff have a mind of peace to focus on research quality, and focus on their research's impact on society; (III) we all know fair competition is good and monopoly is bad. Without highly skilled and decentralized management, big institutions can create hurdles for flexibility, proactiveness, and initiations. Research collaboration is often more facilitated by geographical closeness and cultural closeness rather than being under a single administrative umbrella. If the University of Hong Kong, the Chinese University of Hong Kong, and the Hong Kong University of Science and Technology are to be merged into a single mega-university, the total out-put will be likely to be less given the same investment. To foster competition, the government of Singapore created another new medical school in Nanyang Technological University so to compete with the medical school at the National University of Singapore. The location of the Indian Institutes of Technology campuses was chosen to be spread throughout India to prevent regional imbalance.

In any case, we should not be too dismayed for our historical track record after all. Even very recently, the Chinese race produced very capable talents like Terence Tao and Patrick Soon-Shiong. We can safely assume that human capabilities follow the statistical *normal distribution*, and there will always be the lucky ones, though maybe few, at the right side of the curve. There are many other ways we can improve our care for the sick at present. As Charles Darwin [1809-1882] remarked "*If the misery of the poor be caused not by the laws of nature, but by our institutions, great is our sin*" (*Voyage of the Beagle*). I would also like to copy it and make a modification so that it to be: "*If the misery of the* *sick be caused not by the laws of nature, but by our institutions, great is our sin*". I end the discussion with this quote: "*A story is told that the medieval stone masons who carved the gargoyles that adorn the great Gothic cathedrals. Sometimes their creations were positioned high upon the cathedral, hidden behind cornices or otherwise blocked from view, invisible from any vantage point on the ground. They sculpted these gargoyles as carefully as any of the others, even knowing that once the cathedral was completed and the scaffolding was taken down, their work would remain forever unseen by any human eye…That, written in a thousand variations, is the story of human accomplishment*" [Murray, (3), p.458].

Disclosure:
(I) I have chosen the 10 reference journals mainly for convenience as these 10 reference journals have been used in Zhang *et al.*'s recent paper. These are good journals but not extremely competitive. To choose these 10 reference journals also make sense to the author because they cover a number of disciplines, and publish both experimental and clinical studies, but with a concentration on hematology. While China has a good track recording in doing hematology research (with works on arsenic trioxide and all-trans retinoic acid) and a good share of resource was invested in this area. The primary purpose of this paper is not to compare investment against R&D, nor to provide comparison across countries. Metric literature data is not a good way to measure a country's research capability; (II) I generated the graphs in this article for the purpose of illustrate the trends and concepts; they are not meant for being exactly precise;

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Appendix 1

Selected examples of international research integration (contents are cited from wikipedia.org).

(I) The European Molecular Biology Laboratory (EMBL) is financially supported by 21 member states, three prospect and two associate member states. Research at EMBL is conducted by approximately 85 independent groups. The Laboratory operates from five sites: the main laboratory in Heidelberg, and outstations in Hinxton (England), Grenoble (France), Hamburg (Germany), and Monterotondo (Italy). EMBL perform basic research in molecular biology and molecular medicine as well as training for scientists and students. The organization aids in the development of services, new instruments and methods, and technology for its member states;

(II) The Fraunhofer Society is a German research organization with 67 institutes spread throughout Germany, each focusing on different fields of applied science. The Society earns about 70% of its income through contracts with industry or specific government projects. The other 30% of the budget is sourced in the proportion 9:1 from federal and state government grants and is used to support preparatory research. Thus the size of the society's budget depends largely on its success in maximizing revenue from commissions. This serves both to drive the realisation of the society's strategic direction of becoming a leader in applied research as well as encouraging a flexible, autonomous and entrepreneurial approach to the society's research priorities. The Fraunhofer Society also operates seven US-based Centers: (i) Coatings and Laser Applications; (ii) Experimental Software Engineering; (iii) Laser Technology; (iv) Molecular Biotechnology; (v) Manufacturing Innovation; (vi) Sustainable Energy Systems; and (vii) Digital Media Technologies. Fraunhofer UK Research Ltd is located in Glasgow, Scotland;

(III) The Japanese pharmaceutical company *Takeda* has R&D sites in Osaka and Tsukuba, Japan; San Diego and San Francisco, United States; Cambridge, United Kingdom; and Singapore;

(IV) The Japanese pharmaceutical company *Eisai* has medical research headquarters in Woodcliff Lake, New Jersey, USA, as well as locations in Japan, the United Kingdom, the Research Triangle in North Carolina, and Massachusetts, USA, where the Eisai Research Institute is based;

(V) The Toshiba America Medical System's executive Team as of March 26, 2015 included Fredric Friedberg, Shuzo Yamamoto, Ryo Fujimoto, Lawrence Dentice, Calum Cunningham, Karen La Point, Mark Mindell, Ted Nemetz, John Patterson, and Nader Rad;

(VI) In 2011 Japan's cabinet approved Okinawa Institute of Science and Technology (OIST), a Japanese graduate school backed by the likes of Nobel Laureates Sydney Brenner, Susumu Tonegawa, Jerome Friedman, and others. OIST supporters want to shake up Japan's universities by creating a new academic model emphasizing interdisciplinary research, and to attract non-Japanese faculty members by using English for teaching and administrative affairs. Jonathan Dorfan becomes the university's first president. Currently over half of the faculty and students are recruited from outside Japan, and all education and research is conducted entirely in English;

(VII) In 2011, a bid by a consortium of Cornell University, USA, and Technion (Israel Institute of Technology), Israel, won a competition to establish a new high-tier applied science and engineering institution in New York City, USA. The new 'School of Genius' in New York City is named the Jacobs Technion-Cornell Institute. The collaboration of Technion with Cornell University is seen as representing a paradigm shift in global education initiatives;

(VIII) *Airbus Industrie* was formed by an initiative between France, Germany and the UK. Its initial shareholders were the French company *Aérospatiale* and the German company *Deutsche Airbus*. *Aérospatiale* and *Deutsche Airbus* each took a 36.5% share of production work, *Hawker Siddeley* (UK) 20% and the Dutch company *Fokker-VFW* 7%. In 1971 the Spanish company *CASA* acquired a 4.2% share of *Airbus Industrie*. In 1979 *British Aerospace*, which had absorbed *Hawker Siddeley*, acquired a 20% share of *Airbus Industrie*.

Supplementary 1

Central Events in Medicine during 1851-1950 (*Murray C, Human Accomplishment: The Pursuit of Excellence in the Arts and Sciences, 800 B.C. to 1950.* Page 213-214).

- 1901: Netherlands, Gerrit Grijns discovers that the cause of beriberi is removal of an essential nutrient in polished rice.
- 1902: USA, Alexis Carrel introduces suturing for blood vessels.
- 1903: Netherlands, Willem Einthoven invents the forerunner of the electrocardiogram.
- 1904: Germany, Alfred Einhorn invents Novocaine.
- 1905: Germany, Fritz Schaudinn and Erich Hoffmann discover the spirochete pallida, the cause of syphilis.
- 1906: England, Frederick Hopkins discovers that food contains ingredients essential to life that are not proteins or carbohydrates, leading to the discovery of vitamins.
- 1909: Germany Japan, Paul Ehrlich and Sahachiro Hata discover salvarsan, an effective treatment for syphilis, founding modern chemotherapy.
- 1910: USA, Frank Woodbury introduces iodine as a disinfectant for wounds.
- 1911: USA, Russell Hibbs conducts a successful spinal fusion operation.
- 1913: USA, Elmer McCollum and Marguerite Davis discover and isolate vitamin A.
- 1915: Japan, K. Yamagiwa and K. Ichikawa identify the first carcinogen by exposing rabbits to coal tar.
- 1916: USA, Jay McLean discovers the anti-coagulant heparin.
- 1920: USA, Harvey Cushing and W. T. Bowie introduce cauterization of blood vessels in surgery.
- 1921: Canada, Frederick Banting, Charles Best, and James Collip invent a method for isolating insulin and injecting it in patients.
- 1921: USA, Elmer McCollum and Edward Mellanby discover an antiricketic substance in cod liver oil and name it vitamin D
- 1926: USA, George Minot and William Murphy successfully treat pernicious anemia with liver.
- 1928: England, Alexander Fleming discovers penicillin, the first antibiotic.
- 1928: USA, George Papanicolaou invents the pap test for diagnosing uterine cancer.
- 1929: USA, Philip Drinker, Louis Shaw, and Alexis Carrel invent an artificial respirator (the iron lung).
- 1932: Germany, Gerhard Domagk discovers that prontosil has antibacterial properties.
- 1934: USA, John and Mary Gibbon invent a heart-lung machine.
- 1938: England, Philip Wiles conducts a total artificial hip replacement, using stainless steel.
- 1939: England, Howard Florey and Ernst Chain isolate the antibacterial agent in penicillin mold.
- 1939: USA, Karl Landsteiner, Philip Levine, and Alexander Weiner discover the connection between the RH factor and pathology in newborns.
- 1941: USA, André Cournand, Werner Forssmann, and Dickinson Richards Germany introduce cardiac catheterization.
- 1943: USA, Selman Waksman, William Feldman, and Corwin Hinshaw discover streptomycin, the first antibiotic effective in treating tuberculosis.
- 1943: USA, Willem Kolff invents the dialysis machine.
- 1944: USA, Alfred Blalock, Helen Taussig, Vivien Thomas, and Edgar Sanford conduct the first “blue baby” operation, correcting the blood supply to the lungs of an infant.
- 1945: USA, John Frisch and Francis Bull initiate the fluoridation of water.
- 1948: USA, Benjamin Duggar and Albert Dornbush discover the tetracycline group of antibiotics.
- 1950: USA, Richard Lawler conducts a successful kidney transplant between two live humans.

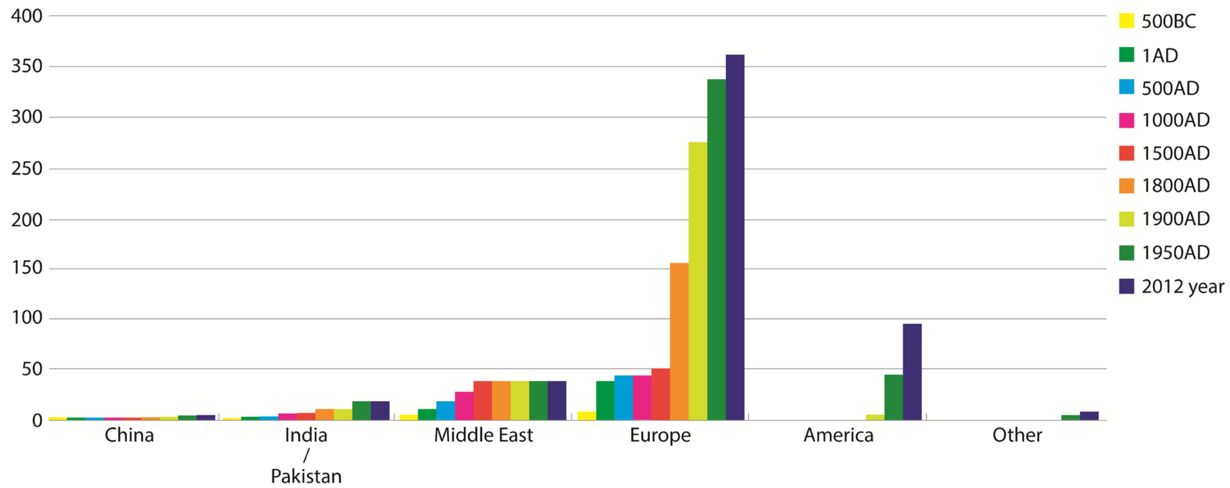

Figure S1 Graphic demonstration of historic periods of China and other civilizations. The accumulative scientific achievement items by various regions at various time-points in history (from BC3000 to year 2012, totaling 515 items). Adapted with permission from Dong *et al*. 2014, reference (11). This figure partially reflects the geographical isolation of China.

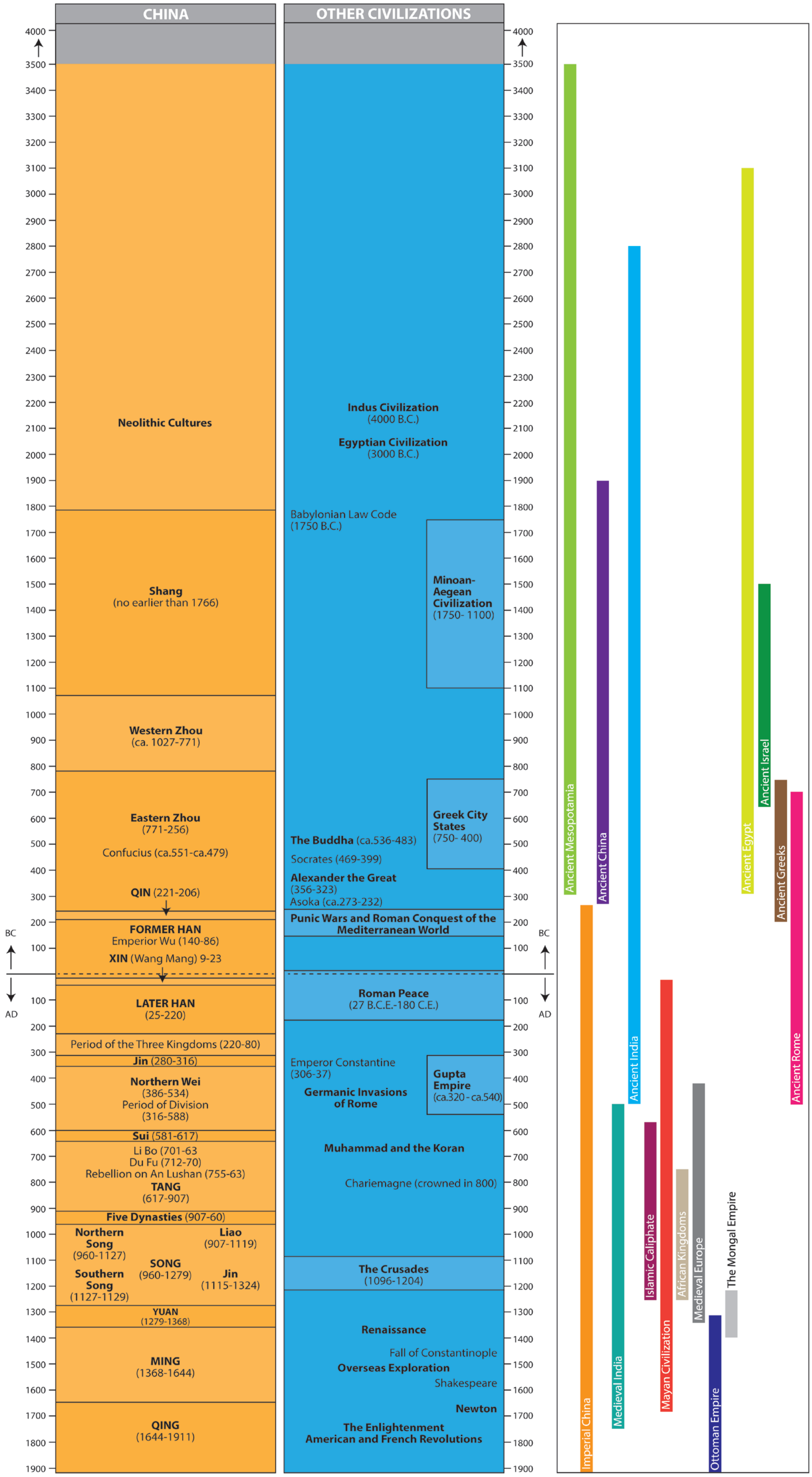

Figure S2 Historic periods of China and other civilizations. Adapted from: webspace.utexas.edu; www.biega.com; www.ancienthistory.about.com.