The 11th Joseph Needham Memorial Lecture
Chinese Medicine: A Journey Through the Ages

The 130th Anniversary of the Faculty of Medicine, HKU
March 24, 2017, at the 22nd anniversary of his death.

Joseph Needham FRS, FBA, Companion of Honor, UNESCO Einstein Gold Medal, Order of Brilliant Star from Taiwan and Hon Prof of Chinese Academy of Sciences and Chinese Academy of Social Sciences; Sir William Dunn Reader in Biochemistry and Master of Caius College, Cambridge. He conducted a comprehensive comparative study of the history of Chinese science and technology relative to the rise of modern science and his work in the “Science and Civilization in China” series served as the foundation for The East Asia History of Science Library and The Needham Research Institute in Cambridge.

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The New Stone Age, BC 7000-5000, produced "Shen Nong" (神農), the Sun God, who was the "God of Herbs". Around BC 5000-4000, "Huang Di" (黃帝), with minister, Qi Bo (岐伯), documented, the causes, diagnosis and treatment with 100 herbal formulae. In 2011, UNESCO listed “Huang Di Nei Jing” (Inner Canon of the Yellow Emperor) (《黃帝內經》) and "Ben Cao Gang Mu" (The Compendium of Materia Medica) (《本草綱目》) as Memory of the World.

More than 2,000 years of Chinese civilization from the Warring States to China today has witnessed economic and social changes which impacted on the development of the practice of medicine. Classical archives and reviews were turned into medical encyclopedia, and pharmacopeia. The journey of development is examined from modern western medicine viewpoint on the pioneering landmarks in the following domains:

1. **Pharmacology** – “The Canon of Herbal Medicine” (《神農本草經》) BC221-AD 221, documented 365 medicines classified into high, medium and low quality, with documentation of herb-herb interaction, standards of harvest time, production, storage and formulation. There were records of objective evaluation of treatment outcome in relation to the timing of administration.

2. **Personal Health** – “Food as Preventive Medicine" (藥食同源) BC1648-1549, documented the use of decoction in lowering the toxicity by the use of boiling of herbs together. The theory of using food as medicine in keeping healthy was established then. Confucius BC551-479, expounded the importance of good eating habits and mental health in achieving resilience and happiness. The Seven Sages of the Bamboo Grove (竹林七賢) emphasized the 'mind body spirit' management especially in the use of music therapy.

3. **Acupuncture & Meridian** – The “Bian Que School” (扁鵲學派) BC401-310, established the 4 diagnostic steps (四診) of inspection, auscultation, history taking and pulse diagnosis. The meridians, acupuncture points and methodology were recorded in the "Huang Di 81 Nan Jing" (《黃帝八十一難經》)
The July 2017 Newsletter of The GP-TCM Research Association

4. **Chinese Medicine Theories & Practice – Chun Yu Yi (淳于意), BC 205-150, created the Medical Records System (診籍) and the Case Study Principles & Practice. He used Pulse Diagnosis to analyze the etiology, the condition and prognosis.**

5. **Surgery & Anesthesia – Hua Tuo (華佗) AD 145-208, “The Saint” used Anesthesia & Antiseptic for drainage of abscess from a bone of a famous General, Guan Yu (關羽). He established the “Mind Body Guidance: Tiger, Deer, Bear, Chimpanzee & Bird” (五禽戲), as an exercise for prevention & rehabilitation.**

6. **Medical Ethics – “Spring in the Apricot Forest” (杏林春暖) AD200-280, Dong Feng (董奉), did not take money for his service but asked his patients to plant apricots trees. When spring arrived, the apricots were sold to exchange for rice which were given to the poor. The seeds would be used as medicine. This sets the standard of practice of medicine to help the world.**

7. **Public Health & Infectious Diseases – In the “Inner Chapters of the Minimalist” (《抱樸子內篇》), Ge Hong (葛洪) AD283-343, described the treatment of malaria using Artemisia carvifolia of Nobel Prize fame. Prof Needham went to great length to find proof that smallpox vaccination started in China. The “Golden Mirror of Smallpox” AD 1579, described the deaths from vaccine using scabs from severe smallpox.**

8. **Specialties – “Arcane Essentials from the Imperial Library” (《外台秘要》) contained special section on Gynecology, Pediatrics, Infectious Diseases and Ophthalmology. It contained the earliest record of removal of cataract by the use of gold needles.**

9. **Forensic Medicine – “Bronze ladle on Judge Bai” (《白揚父岐山之匜》) BC820 and “Monthly Ordinance” (《月令》) BC300 were early documents on methodology and law on forensic investigation. “Washing away the Wrongs” (《洗冤錄》) by Song Ci (宋慈) AD186-1249, was the earliest compendium on Forensic Medicine. This has been translated into Korean in 1384, Japanese in 1768, French 1779 and English in 1855.**

10. **Medical Administration and Examination – Emperor Han Wen (漢文帝) BC 165-124, established “National University” with Professors of Medicine and Lecturers as assistants. By AD 723, Provincial Colleges of Medicine were built with “101 Proven Medicinal Formulae” (《百一集驗方》) and “Formulae for Widespread Benefaction” (《廣濟方》), for public use. This is similar to the Essential Drug list prepared by WHO nowadays. A “National Administration for Health” was created in the Sui Dynasty (隋朝) AD 581-618 and “National Administration of Medical Education” (醫學提舉司) in the Yuan Dynasty (元朝) AD 1272, when “Proposal for Model Examination Papers” described the 13 courses, the 6 types of exam questions and an assessment by clinical outcome of patients which were linked with salary increase and contract renewal.**

The stories of iconic teachers associated with their scholarly archives unravel the myth around traditional Chinese medicine, which, hitherto, have been misinterpreted and misunderstood. Indeed, modern medicine could benefit from following Prof Joseph Needham’s inquisition into the development of scientific theories based in meticulous clinical observation and logical deduction.
Special Features


     
     "...the CONSORT extension for CHM Formulas 2017 is a highly welcome, detailed, and well-structured proposal. Developed by experienced clinical and methodological experts over several years, it has the potential to greatly improve the design of as well as the reporting on interventions in RCTs. The well-balanced inclusion of important aspects of TCM theories, such as Pattern diagnosis, and the careful description of how to define the CHM formulas in study interventions will help interpret study results not only from the Western perspective but also from the TCM perspective. Unlike the CONSORT extension for acupuncture, the CHM extension does not require reporting the training and experience of the persons making the Pattern diagnosis and TCM prescriptions. This might be an item for a future update because it can be relevant for assessing the quality of the intervention. Reporting all details required in the recommendations will need considerable publication space. Some of the reporting may have to be done in online appendices of the main trial publications..."
     
     [Link to the article](http://annals.org/aim/article/2633847/randomized-trials-chinese-herbal-medicine-new-extension-consort-statement)

     
     Chinese herbal medicine (CHM) formulas are the major components of traditional Chinese medicine (TCM) interventions. The general reporting quality of randomized controlled trials (RCTs) of CHM formulas is disappointing, although CONSORT (Consolidated Standards of Reporting Trials) Statement extensions for herbal medicinal interventions and acupuncture interventions are available. A group of TCM clinical experts, methodologists, epidemiologists, and editors has developed this CONSORT Extension for CHM Formulas (CONSORT-CHM Formulas 2017) through a comprehensive process, including publication of the draft version, solicitation of comments, revision, and finalization. The CONSORT 2010 Statement was extended by introducing the idea of TCM Pattern and the features of CHM formulas. One new checklist subitem, keywords, was added to facilitate indexing and data searching. Seven of the 25 CONSORT checklist items, namely title and abstract, background and objectives, participants, interventions, outcomes, generalizability, and interpretation, are now elaborated, and the explanation of harms specific to CHM formulas is revised. Illustrative examples and explanations are also provided. The group hopes that CONSORT-CHM Formulas 2017 can improve the reporting quality of RCTs of CHM formulas.
     
     [Link to the article](http://annals.org/aim/article/2633843/consort-extension-chinese-herbal-medicine-formulas-2017-recommendations-explanation-elaboration)


WeChat report in Chinese: [Link](http://mp.weixin.qq.com/s/FCya6gS69p2vP8nBCZisag)

Related papers in English and Chinese, including editorial, can be downloaded from here: [Link](https://pan.baidu.com/s/1pL9bqH#list/path=%2FCONSORT%20CHM%20formula%202017)
European Reports

1. Report calls for radical shake-up of EU research. Former WTO chief Pascal Lamy sets out a wide range of ideas to reform EU research and innovation programmes, starting a year-long campaign to secure the future research budget. Ideas for a radical overhaul of the next EU research programme, including the binning of one third of all funding schemes and an end to routine audits on researchers, were part of a significant report presented in Brussels on Monday. The study, with the bewildering title – “Lab-Fab-App”, a portmanteau of laboratories, innovation fabrication and applications – proposes several politically sensitive ideas, such as moving more responsibility for EU regional funding into the research programme, devoting more agricultural and regional funding to innovation-related work, and revamping EU state aid rules.

The sweeping set of ideas are presented by 12 figures drawn across research, industry and finance fields, including Martin Brudermüller, chief technology officer with German chemical company BASF; Mark Ferguson, chief science adviser to the Irish government; and Lykke Friis, prorector for education at the University of Copenhagen. The chair of the report, Pascal Lamy, is a former EU trade Commissioner and head of the World Trade Organization.

http://sciencebusiness.net/news/80365/Report-calls-for-radical-shake-up-of-EU-research#.WVuCALV2nXg

2. European quantum physicists bring Schrödinger’s cat to life (and death). A real cat can’t be both alive and dead at the same time, Austrian physicist Erwin Schrödinger said. But quantum physics rewrites the rules, a fact now demonstrated by a team of researchers funded by the EU.

http://cordis.europa.eu/result/rcn/197348_en.html

3. Quantum leap forward in understanding biological processes. EU-funded researchers have successfully applied quantum physics in order to better understand some fundamental biological processes. This ground-breaking work could eventually help industry to develop more efficient light harvesting technologies and artificial odour sensors.

http://cordis.europa.eu/result/rcn/197348_en.html

4. Abbott A. Europe’s next big science-funding programme urged to double its budget. Nature 2017;547:17. Midway through the European Union’s sprawling 7-year, €75-billion (US$85-billion) research-funding programme known as Horizon 2020 (H2020), scientists are already angling for more money and less red tape in its successor. So researchers are delighted with an influential 3 July report that urges the EU to double the budget of its next funding scheme, called Framework Programme Nine (FP9), which is due to launch in 2021. The report says that FP9’s structure should be largely similar to that of H2020, but with less bureaucracy, and suggests that it includes a few major ‘moonshot’ missions in areas such as energy and information technology…


5. Steurs L, et al. Role of the European Union in global health. The Lancet Global Health. 2017;5:e756. Elizabeth Speakman and colleagues (April, 2017)1 propose the development of a European global health strategy. As researchers who have analysed the European Union's (EU's) role in global health in the past, we appreciate a renewed debate on this topic. However, we would like to contest some of the arguments…

http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30212-7/fulltext?elsca1=etoc

6. Jo Johnson, Minister of State for Universities, Science, Research and Innovation, confirmed on the 18th July the UK Government’s commitment to underwrite the funding for all successful bids made by UK applicants for Horizon 2020 projects before the UK exits the EU. He delivered a speech at the formal ratification of the Instruct-ERIC (European Research Infrastructure Consortium) in London. Mr Johnson stressed that the underwrite applies to
both projects that are on-going at the point of the UK's EU exit, and funding that is applied for before the UK's exit and is subsequently successful. He also confirmed that the underwrite includes Horizon 2020 calls with two-stage procedures, as long as the first application is submitted before the UK leaves the EU. The Minister also acknowledged that there are details to be worked on within the wider context of the negotiations. This information is from UK Research Office (UKRO).

7. Has Brexit affected UK participation in H2020? …Initial analysis for 2016/2017 shows that the UK continues to lead the coordinator list with approximately 18% of granted projects. This is a minor decrease from 2014 and 2015 where the UK coordinated 20.8% and 21.2% of the projects. In addition, projects in which the UK is a participant has dropped to 16.8% from 17.7% and 20.1% in 2015 and 2014 respectively. However, a slight decrease can also be seen for other countries with Germany at 10.3% (11.1% in 2015) and Netherlands at 6.1% (6.8% in 2015) as coordinator of granted projects. Meanwhile, a few countries experienced an increase as coordinators, such as France at 8.8% (8.3% in 2015) and Spain at 13.7% (11.2% in 2015). The decline in British coordination is slightly larger than the decline observed in Germany or The Netherlands… Brexit means Brexit? Amidst the platitudes, the UK government has welcomed an agreement to continue collaboration with European partners on science, research, and technology initiatives as a part of the 12 negotiating priorities. This has also been reflected during the general election with the conservative manifesto promising to collaborate in science and innovation while the labour manifesto promising to stay part of H2020 and its successors. Thus, even after Brexit, continued collaboration between UK and EU scientists looks possible and external participation has precedent with the Swiss involvement in H2020. These should hopefully allay fears of British isolation from future EU projects and scientists from the EU and UK should not allow politics in the way of scientific excellence that the collaborations have brought.


EU-China Cooperation Reports and China Reports

1. Hu R et al. China’s Belt and Road Initiative from a global health perspective. The Lancet Global Health. 2017;5:e752-e753. As China implements its 13th 5-year plan for national economic and social development, one might ask how efforts being proposed will affect global health through the so-called Belt and Road Initiative. The Belt and Road Initiative aims to connect the Asian-Pacific Economic Area with the European Economic Area by building up two maritime routes, referred to as the 21st century Silk Road. Thus, although its primary aim relates to trade, the initiative has many implicit influences on global health, some of which we provide insights into here.

http://mp.weixin.qq.com/s/aKkiRXQq7SnkuYc_XhGonA (中文)

2. Choudhury SR. China emerging as a tech and innovation powerhouse. CNBC.com, 18 July 2017. “China’s shift from a country that copies ideas from the West to a tech and innovation powerhouse is no longer an aspiration — it’s a fact. That was the repeated conclusion last week at one of Asia’s largest tech conferences. “China is changing from the so-called copycat nation to innovation nation,” Jing Ulrich, managing director and vice chairman of APAC at JPMorgan Chase, told audiences at the RISE conference in Hong Kong last week. China’s rise in technology has been spurred by the emergence of large companies such as Tencent, Alibaba and Baidu that paved the way for other local firms to follow...” http://www.cnbc.com/2017/07/18/china-emerging-as-a-tech-and-innovation-powerhouse.html?from=groupmessage&isappinstalled=0

3. The Lancet Editorial. Medical education reform in China. Lancet 2017;390:334. On July 11, the State Council of China introduced bold plans to revolutionise medical education, effective immediately. Gone will be Soviet-era training in which doctors spent their career in one hospital, and...
over-crowded outpatient clinics that too often underutilised the expertise of staff and underserved the needs of patients. Instead, medical schools are asked to admit more, higher calibre students, and provide better quality teaching that is accredited by the Chinese Medical Doctor Association. After 5 years of medical school, graduates will enter a 3-year standardised residency programme at the start of specialisation. New 5+3 doctors must demonstrate adequate competencies, confirmed by examination, before a nationally recognised certificate is issued. Once in practice, distance-learning will support life-long professional development. This is arguably the most important directive since medical reform was accelerated in 2009, and will reshape the delivery of care in China.

http://dx.doi.org/10.1016/S0140-6736(17)31921-9
http://www.gov.cn/zhengce/content/2017-07/11/content_5209661.htm (中文)

**TCM and Other Traditional Medicines in Spotlight**

1. **ISO vocabulary on Chinese Materia Medica published in July 2017.** ISO 18662-1:2017 specifies the basic vocabulary for the Chinese Materia Medica (CMM), including most commonly used CMM species. Each term is provided a Latin name, Chinese name, Pinyin name and English name. Source-related definition of applicable parts and botanical name(s) of the plant, zoological family name of the animal, or mineral stated with mineral or rock title and active ingredients are given as note(s) for each item. ISO 18662-1:2017 is intended to be used by those engaged in the practice and management of production, trade, research and education of crude natural Chinese medicinal materials. [https://www.iso.org/standard/63148.html](https://www.iso.org/standard/63148.html)

http://www.worldtcm.org/170722/3Z0015556.shtml?from=groupmessage&isappinstalled=0 (中文)

2. **Selected publications on TCM from Chinese Journal of Natural Medicines in 2017.**

   2.1. **Hu RF, Sun XB. Design of new traditional Chinese medicine herbal formulae for treatment of type 2 diabetes mellitus based on network pharmacology.** *Chin J Nat Med.* 2017;15:436-441. In the present study, 28 Chinese medicinal herbs belonging to TCM for the treatment of type 2 diabetes were selected to explore the application of network pharmacology in developing new Chinese herbal medicine formulae for the treatment of type 2 diabetes mellitus (T2DM). These herbs have the highest appearance rate in the literature, and their compounds are listed. The human protein-protein interaction network and the T2DM disease protein interaction network were constructed. Then, the related algorithm for network topology was used to perform interventions on the interaction network of disease proteins and normal human proteins to test different Chinese herbal medicine compound combinations, according to the information on the interaction of compounds-targets in two databases, namely TarNet and the Medicinal Plants Database. Results of the intervention scores indicate that the method proposed in this study can provide new effective combinations of Chinese herbal medicines for T2DM. Network pharmacology can effectively promote the modernization and development of TCM.


   2.2. **Wang XM, Li XB, Peng Y. Impact of Qi-invigorating traditional Chinese medicines on intestinal flora: A basis for rational choice of prebiotics.** *Chin J Nat Med.* 2017;15:241-254. According to the theory of TCM, Qi (vital energy) is regarded as a driving force of biological activities in human body, including both nutrient substances and organ functions. Qi-invigorating TCMs are widely used to treat various symptoms and disorders, such as fatigue, obesity, immunosuppression, intestinal flora imbalance, and gastrointestinal diseases, in which Qi is considered to be reduced or depleted. Interestingly, abundant clinical evidences suggest that these disorders are associated with the alternation of intestinal flora, which directly affects disease status. Herein we review the interaction between gut microbiota and Qi-invigorating TCMs under healthy and disease conditions and discuss the mechanisms of action and applications of Qi-invigorating TCMs in enhancing health status through microbial alternation. A better understanding of the role of Qi-invigorating TCMs in modulating microbial composition and the association between intestinal microbiota and diseases...
would help reveal the clinical consequences of microbiota alteration and explore opportunities to harness this symbiotic relationship to improve public health.

https://linkinghub.elsevier.com/retrieve/pii/S1875-5364(17)30041-9

2.3. Y Lin, ZA Wu, ML Shao. Evolution of the registration regulations for proprietary Chinese medicines in China. *Chin J Nat Med* 2017;15:4-11. In this review, we provide a comprehensive overview on the registration of proprietary Chinese medicines (PCMs) in China over the past century by examining published literature and historical data. We will examine this evolving administrative practice for PCMs registration in China, which is divided to the following five stages: (1) initial measures (1915–1948); (2) early development (1949–1965); (3) provincial approval and trial implementation of the “approval number” system (1966–1984); (4) legislation and cleanup (1985–1999); and (5) centralized national approval (2000 until now), offering a panoramic view on the characteristics of PCMs registration management in China.


2.4. Graham D. Regulation of proprietary traditional Chinese medicines in Australia. *Chin J Nat Med* 2017;15:12-14. This review article describes the regulation of proprietary Chinese medicines for the Australian market, which may permit many medicines used in Traditional Chinese Medicine to have a simplified process of market access provided that certain criteria for acceptable public safety are met.


3. WeChat: Academician Liu Baoyan on big data and big opportunities (and challenges) for TCM:
http://mp.weixin.qq.com/s/yAMx7Q1IYWodghvNoptsw（中文）

4. 101 materia medica for both dietary and medicinal use announced by China’s Health Family Planning Commission.
http://mp.weixin.qq.com/s/rmoGjmPLGc7Ixe16X4HLg（中文）

5. China’s 2965 regulated medicinal plants.
http://www.chinanews.com/m/sh/2017/07-18/8281036.shtml?from=groupmessage&isappinstalled=0

6. Platform looks to boost TCM quality (Source: Xinhua | May 26, 2017): AN online regulation platform for traditional Chinese medicine (TCM) has opened in Anguo City, Hebei Province. The platform, including third party approval of all medicine and transparent information on all drug producers, is sponsored by Tasly Holding Group, a pharmaceutical company in the nearby port city of Tianjin… “It’s about time to introduce a trustworthy quality regulation system to supervise every step of the production process,” said Yan Xijun, CEO of Tasly Holding Group. The new platform can guarantee access to information on over 60 major production bases. All the drugs on the platform have been tested by a third party organization, to ensure their safety, Yan said…

7. Feature: Flourishing traditional medicine a stepping stone to understanding Chinese culture. (by Xinhua writers Yuan Yue, Yang Shilong; NEW YORK, May 31 (Xinhua): …For decades, TCM has been recognized as an alternative therapy in the United States. The treatment is included neither in the country's medical system, nor in the curricula of most of its medical schools. Yet demands for TCM, and acupuncture in particular, has been on the rise. Only four states in America to date do not have legislation on professional practices of TCM. It has grown into an industry with 40 thousand licensed therapists, and treats over 380 million patients every year…
http://news.xinhuanet.com/english/2017-06/01/c_136329554.htm

8. Xiong ZH et al. Therapeutic Observation of Abdominal Electroacupuncture plus Chinese Medicinal Application at Umbilicus for Poststroke Constipation [J]. Shanghai Journal of Acupuncture and Moxibustion, 2017, 36(3):265–268. Electroacupuncture combined with Chinese herbal medicine navel paste outperforms drugs for alleviating post-stroke constipation. In a controlled investigation, acupuncture plus topical herbal medicine had a higher total effective rate and a higher
complete recovery rate than drug therapy. In addition, acupuncture plus topical herbal medicine had a significantly lower failure rate than drug therapy.


9. WeChat: A TV series on Yellow Emperor’s Canon of Internal Medicine.
http://873813619.scene.eqh5.cn/s/l4fglwbp (中文)

Omics in Progress

1. The Lancet. Public genomes: the future of the NHS? Lancet 2017;390:203 . On July 4, Sally Davies, the UK Chief Medical Officer, issued her annual report. Entitled “Generation Genome”, the report examines the potential for genomics to form a major part of British health policy in the future. The report offers a wide-ranging view of current and future uses of genomic science, and provides an update on the UK Government’s undertaking, in 2012, to sequence 100 000 whole genomes, the 100 000 Genome Project, and make Britain a world leader in genomic medicine. The report details, for example, how genomic medicine is making strides in the field of rare diseases, which collectively affect 7% of the UK population. The report also lays out the economic case, highlighting that the cost of whole genome sequencing has fallen from US$5500 per genome when the 100 000 Genome Project began 5 years ago to around $1000 now...

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31859-7/fulltext?elsca1=etoc

Professor Dame Sally Davies said: “The age of precision medicine is now and the NHS must act fast to keep its place at the forefront of global science. This technology has the potential to change medicine forever but we need all NHS staff, patients and the public to recognise and embrace its huge potential. Genomic medicine has huge implications for the understanding and treatment of rare diseases, cancer and infections - ending the 'diagnostic odyssey' and tailoring treatment for more patients than ever before. Patients with cancer or a rare disease should have access to genomics-based care, and health and care professionals should consider this as a standard part of their approach.” Her report can be found here: https://www.gov.uk/government/publications/chief-medical-officer-annual-report-2016-generation-genome

2. Northcott PA, et al. The whole-genome landscape of medulloblastoma subtypes. Nature 2017;547:311-7. Summary: Genomic analysis of 491 medulloblastoma samples, including methylation profiling of 1,256 cases, effectively assigns candidate drivers to most tumours across all molecular subgroups. Abstract: Current therapies for medulloblastoma, a highly malignant childhood brain tumour, impose debilitating effects on the developing child, and highlight the need for molecularly targeted treatments with reduced toxicity. Previous studies have been unable to identify the full spectrum of driver genes and molecular processes that operate in medulloblastoma subgroups. Here we analyse the somatic landscape across 491 sequenced medulloblastoma samples and the molecular heterogeneity among 1,256 epigenetically analysed cases, and identify subgroup-specific driver alterations that include previously undiscovered actionable targets. Driver mutations were confidently assigned to most patients belonging to Group 3 and Group 4 medulloblastoma subgroups, greatly enhancing previous knowledge. New molecular subtypes were differentially enriched for specific driver events, including hotspot in-frame insertions that target KBTBD4 and ‘enhancer hijacking’ events that activate PRDM6. Thus, the application of integrative genomics to an extensive cohort of clinical samples derived from a single childhood cancer entity revealed a series of cancer genes and biologically relevant subtype diversity that represent attractive therapeutic targets for the treatment of patients with medulloblastoma.

http://www.nature.com/nature/journal/v547/n7663/full/nature22973.html?WT.ec_id

4. Schaefer KA, et al. Unexpected mutations after CRISPR-Cas9 editing in vivo. Nat Methods. 2017;14:547-548. It's been hailed as one of the most potentially transformative inventions in modern medicine, bringing the prospect of designer babies closer than any other technology to date, but CRISPR-Cas9 could be riskier than we thought. The technology that could spark a gene-editing revolution has been caught introducing hundreds of unintended mutations into the genome, and with scientists already testing it in humans, it's set off some serious alarm bells. The abstract of this Nat-Methods paper reads: "CRISPR–Cas9 editing shows promise for correcting disease-causing mutations. For example, in a recent study we used CRISPR-Cas9 for sight restoration in blind rd1 mice by correcting a mutation in the Pde6b gene. However, concerns persist regarding secondary mutations in regions not targeted by the single guide RNA (sgRNA). Algorithms generate likely off-target sites for a given gRNA, but these algorithms may miss mutations. Whole-genome sequencing (WGS) has been used to assess the presence of small insertions and deletions (indels) but not to probe for single-nucleotide variants (SNVs) in a whole organism. We performed WGS on a CRISPR–Cas9-edited mouse to identify all off-target mutations and found an unexpectedly high number of SNVs compared with the widely accepted assumption that CRISPR causes mostly indels at regions homologous to the sgRNA." https://www.sciencealert.com/turns-out-crispr-gene-editing-can-cause-hundreds-of-unexpected-mutations
http://mp.weixin.qq.com/s/_QEfbWJ5MDXWIApGlnTRbg (中文)

BUT, this work was quickly criticised for many careless mistakes in the Pubmed Commons: https://www.ncbi.nlm.nih.gov/myncbi/xiaolin.wu.1/comments/

5. Kuscu C, et al. CRISPR-STOP: gene silencing through base-editing-induced nonsense mutations. Nat Methods. 2017;14:710-712. CRISPR-Cas9-induced DNA damage may have deleterious effects at high-copy-number genomic regions. Here, we use CRISPR base editors to knock out genes by changing single nucleotides to create stop codons. We show that the CRISPR-STOP method is an efficient and less deleterious alternative to wild-type Cas9 for gene-knockout studies. Early stop codons can be introduced in ~17,000 human genes. CRISPR-STOP-mediated targeted screening demonstrates comparable efficiency to WT Cas9, which indicates the suitability of our approach for genome-wide functional screenings. https://www.nature.com/nmeth/journal/v14/n7/full/nmeth.4327.html

6. Cameron P, et al. Mapping the genomic landscape of CRISPR-Cas9 cleavage. Nat Methods. 2017;14:600-606. NA-guided CRISPR-Cas9 endonucleases are widely used for genome engineering, but our understanding of Cas9 specificity remains incomplete. Here, we developed a biochemical method (SITE-Seq), using Cas9 programmed with single-guide RNAs (sgRNAs), to identify the sequence of cut sites within genomic DNA. Cells edited with the same Cas9-sgRNA complexes are then assayed for mutations at each cut site using amplicon sequencing. We used SITE-Seq to examine Cas9 specificity with sgRNAs targeting the human genome. The number of sites identified depended on sgRNA sequence and nuclease concentration. Sites identified at lower concentrations showed a higher propensity for off-target mutations in cells. The list of off-target sites showing activity in cells was influenced by sgRNP delivery, cell type and duration of exposure to the nuclease. Collectively, our results underscore the utility of combining comprehensive biochemical identification of off-target sites with independent cell-based measurements of activity at those sites when assessing nuclease activity and specificity. https://www.ncbi.nlm.nih.gov/pubmed/28459459


9. Liu X, et al. The genome of the medicinal plant Macleaya cordata provides new insights into benzylisoquinoline alkaloids metabolism. *Mol Plant.* 2017;10:975-989. The overuse of antibiotics in animal agriculture and medicine has caused a series of potential threats to public health. Macleaya cordata is a medicinal plant species from the Papaveraceae family, providing a safe resource for the manufacture of antimicrobial feed additive for livestock. The active constituents from M. cordata are known to include benzylisoquinoline alkaloids (BIAs) such as sanguinarine (SAN) and chelerythrine (CHE), but their metabolic pathways have yet to be studied in this non-model plant. The active biosynthesis of SAN and CHE in M. cordata was first examined and confirmed by feeding 13C-labeled tyrosine. To gain further insights, we de novo sequenced the whole genome of M. cordata, the first to be sequenced from the Papaveraceae family. The M. cordata genome covering 378 Mb encodes 22,328 predicted protein-coding genes with 43.5% being transposable elements. As a member of basal eudicot, M. cordatagénomemelaks the paleohexaploidy event that occurred in almost all eudicots. From the genomics data, a complete set of 16 metabolic genes for SAN and CHE biosynthesis was retrieved, and 14 of their biochemical activities were validated. These genomics and metabolic data show the conserved BIA metabolic pathways in M. cordata and provide the knowledge foundation for future productions of SAN and CHE by crop improvement or microbial pathway reconstruction. [http://www.sciencedirect.com/science/article/pii/S1674205217301399](http://www.sciencedirect.com/science/article/pii/S1674205217301399)


11. Kazazian HH Jr, Moran JV. Mobile DNA in Health and Disease. *N Engl J Med.* 2017;377:361-370. The completion of the Human Genome Project has enabled the identification of many genes, including variants that cause disease. An important discovery, although less celebrated, is that more than half the human genome is derived from mobile pieces of DNA called transposable elements (colloquially known as “jumping genes”). Transposable elements were discovered in corn by Barbara McClintock more than 60 years ago, but few people would have guessed that the aggregate length of these sequences exceeds that of protein-coding exons by a factor greater than 40. Although the bulk of transposable element–derived DNAs are remnants of their former selves and cannot transpose, some retain the ability to mobilize. The insertion of mobile elements into the DNA of gametes or the early embryo can disrupt genes, leading to sporadic cases of disease, and their insertion into the DNA of somatic cells may contribute to cancers and neuropsychiatric disease. Clearly, mobile DNA has been instrumental in shaping the structure, function, and evolution of the human genome. Here we discuss the biology of mobile DNA, emphasizing key discoveries that illustrate how it contributes to human disease. [http://www.nejm.org/doi/10.1056/NEJMra1510092](http://www.nejm.org/doi/10.1056/NEJMra1510092)

Other Recommended Readings

1. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *Lancet.* 2017;390:415-423. In response to limitations in the understanding and use of published evidence, evidence-based medicine (EBM) began as a movement in the early 1990s. EBM's initial focus was on educating clinicians in the understanding and use of published literature to optimise clinical care, including the science of systematic reviews. EBM progressed to recognise...
limitations of evidence alone, and has increasingly stressed the need to combine critical appraisal of the evidence with patient's values and preferences through shared decision making. In another progress, EBM incorporated and further developed the science of producing trustworthy clinical practice guidelines pioneered by investigators in the 1980s. EBM's enduring contributions to clinical medicine include placing the practice of medicine on a solid scientific basis, the development of more sophisticated hierarchies of evidence, the recognition of the crucial role of patient values and preferences in clinical decision making, and the development of the methodology for generating trustworthy recommendations...

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)31592-6/fulltext?elsca1=etoc

2. Lund H, et al. Towards evidence based research. BMJ. 2016 Oct 21;355:i5440. To avoid waste of research, no new studies should be done without a systematic review of existing evidence, argue Hans Lund and colleagues. They wrote: "Whether or not today's medical researchers, like Isaac Newton, see themselves as “standing on the shoulders of giants,” they might still be expected to build systematically on previous research when planning new studies. Even though this issue was highlighted as early as 2005,1 2 numerous studies indicate that researchers do not use a systematic methodology to identify and refer to earlier research when justifying, designing, or discussing new research.3 4 5 6 7 8 9 10 11 This is true, even in high quality clinical studies published in the most prestigious medical journals.4 5 8 12 Rather, medical researchers select studies to cite based primarily on preferences and strategic considerations.13 14 15 16 17 18 The term “evidence based research” was coined in 2009 to indicate the approach that is needed to reduce this practice, which is an important source of research waste19 and risks unnecessary harm for patients and study participants…” http://www.bmj.com/content/355/bmj.i5440.long

https://mp.weixin.qq.com/s/PwgXjfdrk9Pmu9GJhKcFsA?scene=25#wechat_redirect (中文)

3. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017;377:62-70. High-quality evidence is what we use to guide medical practice. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of “precision medicine” trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time. A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure. Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions...

http://mp.weixin.qq.com/s/UMPPCnufuyNgPpkI4nqFqQ (中文)

4. Gregg EW and Shaw JE. Global Health Effects of Overweight and Obesity. N Engl J Med 2017; 377:80-81. The Global Burden of Disease (GBD) study that is now reported in the Journal offers a discouraging reminder that the global obesity epidemic is worsening in most parts of the world and that its implications regarding both physical health and economic health remain ominous. The study, in which researchers assembled data from 195 countries to model trends in overweight and obesity and related morbidity and mortality, showed that the prevalence of obesity has more than doubled since 1980 and is now 5% in children and 12% in adults — findings that mirror similar global trends in type 2 diabetes. Apart from a possible recent plateau in the prevalence of obesity in high-income countries, the prevalence has increased in all other sociodemographic strata...


5. GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med.* 2017;377:13-27. Although the rising pandemic of obesity has received major attention in many countries, the effects of this attention on trends and the disease burden of obesity remain uncertain. We analyzed data from 68.5 million persons to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. Using the Global Burden of Disease study data and methods, we also quantified the burden of disease related to high body-mass index (BMI), according to age, sex, cause, and BMI in 195 countries between 1990 and 2015. Results: In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to cardiovascular disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from cardiovascular disease. Conclusions: The rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem.


Another report in the same issue of *NEJM* confirmed that the sudden death rate of cardiac diseases significantly reduced (44%) in the past 15-20 years:


*Sci Transl Med:* http://stm.sciencemag.org/content/9/394/eaah4477

7. MicroRNAs in pain regulation. Pain is not something universally enjoyed, especially chronic pain involving nerve damage, referred to as neuropathic pain. Pain perception can be modulated in a variety of ways—for example, by focusing attention on the painful stimulus. On page 1168 of this issue, Peng et al report that pain threshold in dorsal root ganglion neurons (DRG), which relay peripheral sensory information to the central nervous system, can be modulated by mechanisms involving a specific cluster of microRNAs (miRNAs). Remarkably, the same cluster also regulates the threshold of neuropathic pain in DRG neurons that would not be involved in pain under normal conditions. The study provides important new insights into molecular mechanisms that control pain threshold, both in normal and pathological conditions.

- Cassels L, Barde YA. **Scaling pain threshold with microRNAs.** *Science* 2017;356:1124–1125.

http://science.sciencemag.org/content/356/6343/1168?ijkey
http://science.sciencemag.org/content/356/6343/1124

8. Mosialou I, et al. **MC4R-dependent suppression of appetite by bone-derived lipocalin 2.** *Nature.* 2017;543(7645):385-390. Bone has recently emerged as a pleiotropic endocrine organ that secretes at least two hormones, FGF23 and osteocalcin, which regulate kidney function and glucose homeostasis, respectively. These findings have raised the question of whether other bone-derived...
hormones exist and what their potential functions are. Here we identify, through molecular and genetic analyses in mice, lipocalin 2 (LCN2) as an osteoblast-enriched, secreted protein. Loss- and gain-of-function experiments in mice demonstrate that osteoblast-derived LCN2 maintains glucose homeostasis by inducing insulin secretion and improves glucose tolerance and insulin sensitivity. In addition, osteoblast-derived LCN2 inhibits food intake. LCN2 crosses the blood-brain barrier, binds to the melanocortin 4 receptor (MC4R) in the paraventricular and ventromedial neurons of the hypothalamus and activates an MC4R-dependent anorexigenic (appetite-suppressing) pathway. These results identify LCN2 as a bone-derived hormone with metabolic regulatory effects, which suppresses appetite in a MC4R-dependent manner, and show that the control of appetite is an endocrine function of bone.

https://www.nature.com/nature/journal/v543/n7645/full/nature21697.html


WeChat commentary: http://mp.weixin.qq.com/s/KiBwaS7MUGePipIhgDrRGw (中文)

9. Green JM et al. Food and microbiota in the FDA regulatory framework. Science 2017; 357: 39-40. New understanding of how our gut microbial communities (microbiota) transform dietary ingredients into metabolic products that affect human biology is altering our definitions of the nutritional value of foods. We are coming to appreciate how much formation of the gut microbiota during early postnatal life and the traits encoded by its several million microbial genes (microbiome) are important determinants of healthy growth and of our metabolic, physiologic, immune, and perhaps neurologic phenotypes. These advances are spawning efforts to develop foods that promote healthy microbiota development during early postnatal life, prevent the loss of microbial diversity associated with Western diets, and repair abnormalities associated with various disease states. But given the mechanisms by which such microbiota-directed foods (MDFs) may achieve their desired effects, the existing U.S. regulatory framework presents challenges in determining how MDFs should be classified. How these challenges are addressed will affect innovation incentives, product quality, consumer access, and public health. Although approaches to regulation vary among countries, we focus on the U.S. Food and Drug Administration (FDA) because of its global influence and because the products it regulates are often widely distributed...

http://science.sciencemag.org/content/357/6346/39.full

Meeting Reports

10. Pharm Exec's Top 50 Companies 2017. Pharm Exec's latest annual listing of the top biopharma players paints a stable picture of performance for the usual placeholders, but change and disruption to current business models could upend positioning in the years ahead. With the exception of a few new bottom-end entrants, and some juggling of positions in the top half, stability remains the name of the game for those biopharmaceutical companies making up this year's list of the industry's top 50 global sales leaders (see tables below). Of course, the relative calm in the rankings meter doesn't mean that stability necessarily begets profitability for all. Amid growing pricing pressures, key patent losses for some, and a slowdown in M&A activity since the middle of 2016, several mainstays on the Pharma 50 list experienced only modest revenue gains in the latest full-year figures collected, while others suffered slight declines. Pharm Exec's 17th annual listing again features data provided by biopharma market intelligence firm Evaluate Ltd.


http://mp.weixin.qq.com/s/fWCizbzetGbZsvKXASsVPA (中文)


http://mp.weixin.qq.com/s/gXjzeKd0G2oKn23TGHmMiw (中文)
Meeting Reports

   http://mp.weixin.qq.com/s/ flZ6AX2ubRTNE_7fmhvOg (中文)

2. WFCMS Network Pharmacology International Forum & the 2nd Meeting of the WFCMS Network Pharmacology Specialty Committee was held in Hefei, Anhui on June 11-12, 2017.
   http://mp.weixin.qq.com/s/81uZV59mRWDwx3Jiam3S8g (中文)

Future Meetings & Events

   http://i.eqxiu.com/s/t0CZ7maU?from=singlemessage&isappinstalled (中文)


3. The 16th Meeting of Consortium for Globalization of Chinese Medicine (CGCM), Guangzhou, China, August 18-20, 2017. This year’s meeting is going to be organized by Guangdong Provincial Hospital of Chinese Medicine. The meeting provides a platform for regulatory-industrial-academic exchanges and potential research collaborations, on various frontiers of Traditional Chinese Medicine among our worldwide CGCM members and guests. You are cordially invited to attend the meetings and submit abstracts. Programme and more details are available on the CGCM website www.tcmedicine.org. Should you have any enquiries, please feel free to contact: centraloffice@tcmedicine.org.

4. Illuminating Biological Systems from a Network Perspective: International Inter-disciplinary Round Table on Biological Networks, September 8th, 2017, University of Namur-Belgium:
   https://easychair.org/conferences/?conf=ibisnet1

5. The Lancet–CAMS Health Summit 2017: A Lancet call for abstracts from China. Abstracts are invited from China for The Lancet–CAMS Health Summit 2017, to be held on Oct 13–14 2017 in Beijing. Submissions are invited from all aspects of health science including, but not limited to: translational medicine, clinical medicine, public health, global health, health policy, the environment and ecological systems and health, health professionalism, and medical education.
   http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30130-7/fulltext?elsca1=etoc

6. WeChat report on international celebration of the 500 anniversary of Li Shizhen’s birth to be held in Li’s homehown Jichun County, Hubei Province, China, on 26th May, 2018.
   http://mp.weixin.qq.com/s?__biz=MzAxMjMyMTEwNA==&mid=2660692447&idx=1&sn=3895e03e994d2f1c98befd9f4beb8eca&chksm (中文)
Invitation from Journals

1. Invitation from World Journal of Traditional Chinese Medicine (WJTCM), including three special calls on TCM network pharmacology, TCM for cerebral disease and TCM for gastrointestinal disease. WJTCM, ISSN 2311-8571, a new peer-reviewed journal (quarterly) launched in 2014, is the official journal of the World Federation of Chinese Medicine Societies (WFCMS) and the GP-TCM RA. **Aim & Scope:** Introduce clinical efficacy and mechanism of TCM to doctors and biomedical researchers around the world, so as to provide new ideas and methods for solving the complicated and difficult cases.

- WJTCM includes reviews and original articles focused on four aspects:
  - Modern Research on Chinese Materia Medica: theories of processing, property, and compatibility of Chinese materia medica; safety of Chinese materia medica; active principles and mechanism and efficacy of crude drugs and Chinese compound formulas
  - Research on TCM Theory: scientific connotation and biological foundation of TCM basic theories
  - TCM clinical Research: disease and syndrome, TCM safety, efficacy evaluation, evidence-based and systematic evaluation
  - Acupuncture and Moxibustion: effect mechanism of acupuncture and moxibustion, specificity of acupoint effect, acupoints compatibility, efficacy evaluation of acupuncture and moxibustion.

**Submission to the Journal:** All the articles can be submitted via ScholarOne: https://mc03.manuscriptcentral.com/wjtcm. Detailed information about requirements of manuscript and format can be found in “Instruction&Forms” by the above URL, or by accessing WJTCM homepage www.wjtcm.org. All WJTCM articles will be published online via WJTCM website (www.wjtcm.org). PDF articles and electronic/online versions are freely available to global readers.

**Special calls on TCM and network pharmacology:**

**Special calls on TCM for cerebral disease:**

**Special calls on TCM for gastrointestinal disease:**

**Sounding Board.**

1. This column is reserved for comments, personal views, proposals for collaborations or any other features from our readers across the world. We look forward to hearing from you! Please get in touch with your editors: Dr Qihe Xu (qihe.xu@kcl.ac.uk), Prof. Pierre Duez (pierre.duez@umons.ac.be) and Prof. Yuan Shun Chang (yschang0404@gmail.com)

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