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In Praise of Remarkably Powerful Centamolecular Therapeutic Agents

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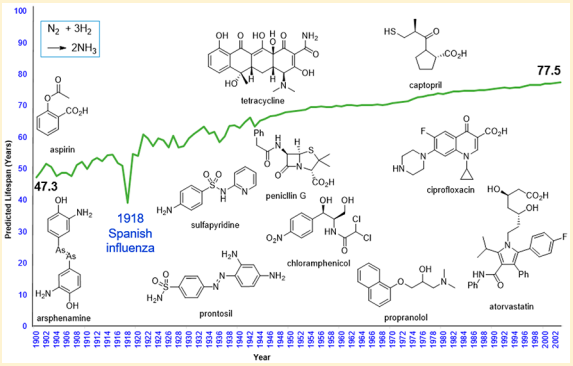
ABSTRACT: While biological medications have addressed many important and challenging therapeutic targets, the pharmacopeia is still dominated by centamolecules. In this Viewpoint, we illustrate the impact of centamolecule drugs on mortality and morbidity due to chronic viral infections and present select examples from other disease areas that highlight some of their remarkably powerful biochemical effects.



EFFECTS OF CENTAMOLECULAR DRUGS ON LONGEVITY AND HUMAN HEALTH

Over the course of the 20th century, life expectancy at birth increased from an average of 47.3 years in 1900 to 77.0 years in 2000, a remarkable 29.7 year (63%) extension in longevity (Figure 1).[1] This development can be attributed to a number

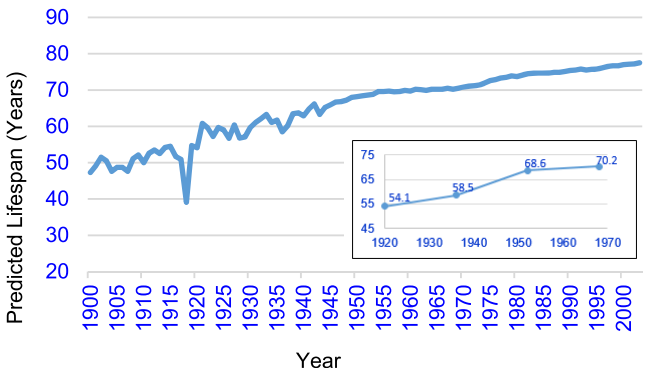


Figure 1. Predicted lifespan at birth in the U.S. between 1900 and 2000. Inset: Predicted lifespan at birth in the U.S. between 1920 and 1968 that compares the 10.1 year increase between 1936 and 1952 with the smaller increases between 1920 and 1936 and 1952 and 1968.

of factors, with the advent of effective drug therapies that treat a range of morbidities and that have led to an enhanced quality of life being a prominent contributor. A particularly important component of the pharmacopeia has been the development of a stable antibiotics that transformed bacterial infections that were frequently life-threatening at the beginning of the 20th century into curable diseases.[2] Between 1936 and 1952, an era that coincided with the development of the four important antibiotic agents, penicillin, prontosil, chloramphenicol, and tetracyclines, predicted lifespan increased by 10.1 years. This value is a markedly higher incremental improvement than the 4.4 and 1.6 year increases in the preceding and succeeding 16 year intervals, respectively, suggesting that the availability of antibiotics underlies 5 to 10 years of increased longevity (Figure 1, inset).[2] The threat of infection on longevity in the absence of effective therapy is most pointedly illustrated by the 11.8 year dip in predicted lifespan that occurred in 1918 as a consequence of the Spanish influenza outbreak that infected an estimated 500 million people worldwide and was responsible for 50 to 100 million deaths (3−5% of the population). Notably, the vast majority of available antibiotics are centamolecules, a modality that continues to dominate the landscape of U.S. Food and Drug Administration (FDA)-approved drugs, amounting to an average of 82% of all of the new molecular entities (NMEs) approved each year between 1993 and 2018 (Figure 2).[3,4]

A more recent demonstration of the capacity of centamolecules to affect mortality and morbidity is provided by the epidemic of human immunodeficiency virus-1 (HIV-1) infection that subtends acquired immunodeficiency syndrome (AIDS) and emerged in the U.S. in 1981. While azidothymidine (AZT, **1**) was approved by the FDA in 1987 as the first therapeutic agent to treat HIV-1 infection, the rapid emergence of resistance to monotherapy limited its therapeutic utility. The full potential of nucleoside analogues was only realized when they were combined with the mechanistically orthogonal HIV-1 protease inhibitors that were introduced in 1995 and 1996, providing centamolecular therapeutic regimens

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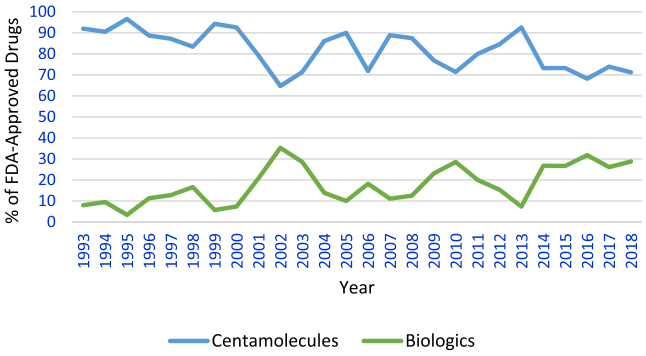

Figure 2. Modality of FDA-approved drugs, 1993−2018.

that led to a rapid and profound 70% decline in the death rate from the peak of 41,388 deaths (~1.5% of the infected population) in 1995 to 12,549 in 1998 (Figure 3).[5] The fall in

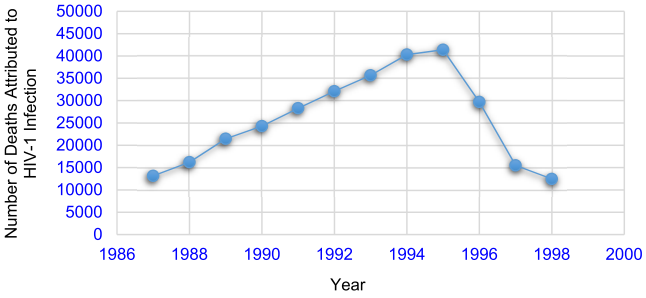

Figure 3. Deaths attributed to HIV-1 infection in the U.S., 1987−1998.

the death rate was more dramatic than the rise, which had seen mortality due to HIV-1 triple over the 8 years following the approval of **1**. HIV-1 infection is now considered to be a manageable, chronic disease that by 2010, when deaths were estimated to be 8,352, was no longer among the top 15 causes of mortality in the U.S.

As mortality due to HIV-1 infection subsided, that from hepatitis C virus (HCV) continued to rise, and by 2007, this chronic viral infection was responsible for more deaths per annum (15,106) in the U.S. than from HIV-1 infection (12,734). This trend continued, and by 2013, 19,368 deaths were attributed to HCV, a number that surpassed those from 60 other reportable infections combined (17,915). In 2012, an analysis based on the extant trajectories predicted that, in the absence of effective therapy, morbidity and mortality due to HCV infection would continue to increase. The peak was predicted to occur between 2030 and 2035, with 38,600 cases of end-stage liver disease, 3,200 referrals for liver transplant (LT), and 36,100 deaths anticipated annually during this period.[6] However, beginning in 2014 the FDA began to approve direct-acting antiviral agents (DAAs), centamolecular therapeutics that, when used in combination, effected HCV cure rates in excess of 95% after just 8−12 weeks of well-tolerated, orally administered therapy. In contrast, the combination of peg-interferon-α and ribavirin that had evolved to be the standard of care by 2014 required 48 weeks of therapy and was associated with a plethora of side effects while achieving only a modest, ~45% cure rate. The effect of DAA combinations was immediate, with the death rate, the number of LTs, and the number of patients placed on the transplant list due to HCV declining rapidly in both the U.S. and Europe.[7,8]

In the U.S., the age-adjusted rate of HCV-related deaths diminished from 5.03 per 100,000 in 2013 to 4.45 per 100,000 in 2016, an 11% decline that predicts a mortality rate of 4.17 per 100,000 by 2020, a 17% reduction from the peak (Figure 4). Commensurate with this, the share of LTs due to HCV

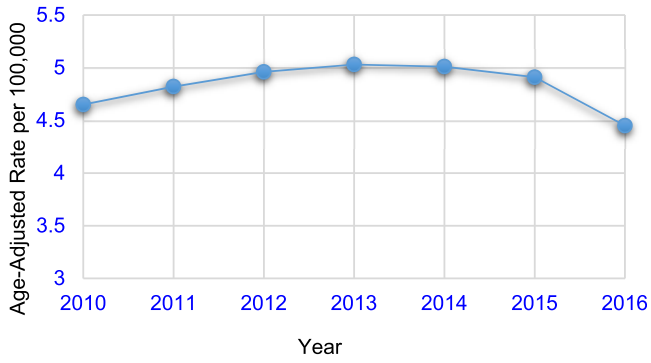

Figure 4. Age-adjusted death rate attributable to HCV infection in the U.S., 2010−2016.

infection has receded, with a 33% decline in 2015, while those attributed to alcohol use and nonalcoholic steatohepatitis (NASH) have continued to rise, with both surpassing HCV as the leading cause of LTs (Figure 5).[7] There has been a similar

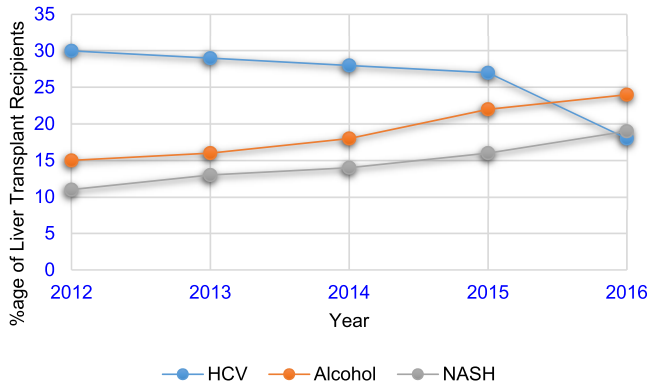

Figure 5. Percentage of liver transplant recipients in the U.S., 2012−2016, based on HCV, alcohol use, or NASH as the underlying cause.

decline in the number of patients waitlisted for LT in the U.S. due to HCV and both of these observations have been fully reflected in studies focused on the experience in Europe.[7,8] While the total number of LTs in Europe remained relatively stable over the 2007−2016 time frame, the complexion based on underlying etiology began to change in 2014, with LTs due to HCV infection declining from 21.1% of the total at the beginning of 2014 to 10.6% at the beginning of 2017, a remarkable 50% decline in just 3 years.[7] Taken together, these developments anticipate a significantly different outlook with respect to HCV-mediated mortality and morbidity to that predicted in 2011.[6,8]

REMARKABLE EFFECTS OF CENTAMOLECULES ON MODULATING BIOCHEMICAL PROCESSES

HCV NS5A inhibitors have emerged as the backbone of contemporary pan-genotype (GT) therapeutic drug combinations, and daclatasvir (**2**), the prototype of this mechanistic class, provides an interesting insight into the remarkable

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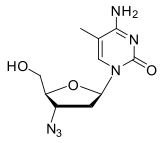
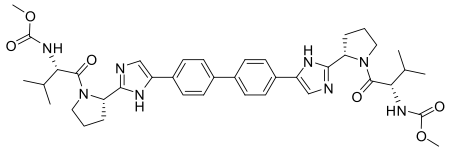
capability of centamolecular drugs to modulate biochemical pharmacology.[9] While the precise function of HCV NS5A remains enigmatic, the protein is an essential component of the virus life cycle and is intimately involved in both the replication of viral RNA and its packaging into the developing virion.



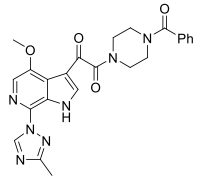
1 (azidothymidine, AZT)



2 (daclatasvir)

While the available evidence indicates that NS5A convenes as a dimer that creates a binding site for viral RNA, higher order oligomers are thought to be the functionally relevant species. HCV NS5A inhibitors are exceptionally potent antiviral agents, and **2** expresses an EC_{50} value of 4 pM toward inhibition of virus replication in a GT 1b replicon.[9] A conservative calculation estimated the concentration of NS5A protein in a cell hosting an active replicon to be 10.6 fg per cell or approximately 189 nM, a 47,000-fold excess over **2** at its EC_{50} concentration. On the basis of **2** engaging a dimeric NS5A protein, the ratio of target to drug exceeds 23,000:1, reflecting the profound impact of a small number of molecules of **2** on the functional activity of a much higher number of NS5A protein dimers.[9] The low level of target engagement required to endow a pharmacodynamic (PD) effect renders HCV NS5A as a biological target of high vulnerability.[10] This kind of phenomenon may extend to other centamolecules that interfere with an oligomeric target, with HIV-1 maturation inhibitors that block cleavage of the Gag-Pol polyprotein at the capsid-spacer peptide 1 junction (CA-SP1) providing an additional example.[11] Preventing the cleavage of <5% of the CA-SP1 protein is sufficient to confer a defect in the capsid structure that acts by a transdominant mechanism to render the virus noninfectious. High target susceptibility also extends to antiviral nucleoside analogues that effect chain termination, either obligate or nonobligate, of a developing oligonucleotide chain, with a 10,000 base pair genome vulnerable to the extent of 1/2,500.

The remarkable effects that centamolecules can exert on biological processes is further illustrated by the HIV-1 inhibitor **3**, the thrombopoietin (TPO) mimetic **4**, and the potential spinal muscular atrophy (SMA) therapeutics **6** and **7**. Temasavir (**3**) binds to HIV-1 gp120 and stabilizes a conformation not recognized by the host cell receptor protein CD4 thereby acting, in part, analogously to the broadly neutralizing antibodies of HIV-1 that have long been sought as potential vaccines.[12] The 332-residue peptide TPO is constitutively excreted primarily by the liver as a heavily glycosylated protein that exerts complex effects on bone marrow, stimulating the proliferation and maturation of megakaryocytes (megakaryocytopoiesis) and acting as the major physiological regulator of platelet production (thrombocytopoiesis).[13] Attempts to develop a pegylated, recombinant version of TPO to treat conditions associated with thrombocytopenia were ultimately unsuccessful due to the production of antibodies that cross-reacted with and neutralized endogenous TPO in 2.4% of 535 normal healthy volunteers, although clinical efficacy was demonstrated. Romiplostim, approved by the FDA in 2003, is a fusion peptide comprising an IgG heavy chain incorporating four, 14-residue TPO agonist peptide moieties that were identified from a random peptide library screen and activate the TPO receptor in a fashion that is competitive with the natural ligand. In contrast, the centamolecule eltrombopag (**4**), which was optimized from a lead discovered by a high-throughput screen (HTS), is a clinically effective and orally bioavailable activator of the TPO receptor that acts as a biased agonist that can bind to the receptor simultaneously with TPO with which it interacts in an additive fashion.[13]



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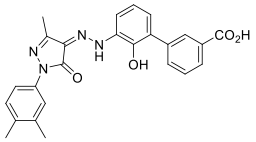

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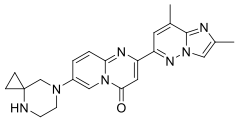
SMA is a devastating disease that is the result of a deficiency of survival motor neuron (SMN) protein due to a homozygous deletion of the *SMN1* gene and had no significant therapeutic option until the approval of the antisense oligonucleotide nusinersen (**5**) in 2016.[14] This 18-mer phosphorothiorate oligonucleotide modulates alternate splicing of the *SMN2* gene to produce the full length mRNA that is translated into SMN protein rather than the truncated variants that are translated as a result of exon skipping and are more rapidly degraded in vivo. Dosing of **5** is by an intrathecal injection consisting of three initial loading doses followed by administration every 4 months. However, two centamolecules, risdiplam (**6**) and branaplam (**7**), that promote the inclusion of exon 7 when the *SMN2* gene is transcribed have been identified by high-throughput phenotypic screens and advanced into clinical study.[14] These molecules are orally bioavailable, distribute readily to the central nervous system, have demonstrated increased production of *SMN2* mRNA and SMN protein in mice and extend the survival of mice in a severe SMA model. Branaplam (**7**) appears to act by enhancing the association of U1 snRNP with *SMN2* pre-mRNA, stabilizing the complex in a fashion that modifies the splicing pattern.[14]

[2′-*O*-(2-$CH_3OCH_2CH_2$)](3′-5′)(*P*-thio)(m^5U-m^5C-A-m^5C-m^5U-m^5U-m^5U-mC-A-m^5U-A-A-m^5U-G-m^5C-m^5U-G-G)

5



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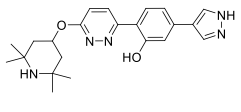

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Centamolecules are being exploited in increasingly creative ways and considerable opportunity exists to discover compounds with effects that will significantly broaden their application in addressing unmet medical need across a range of disease states. Recent examples that include modulation of the trafficking and function of the cystic fibrosis transmembrane conductance regulator, modulators and enhancers of immuno-oncological checkpoint inhibitors, and inducers and inhibitors of protein degradation, an emerging, rapidly growing and promising approach to address "undruggable" targets, anticipate a continuance of centamolecule prominence in drug discovery and development. However, a full understanding of the effect of interactions between centamolecules and

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biomolecules remains elusive, and in order to more fully realize their potential, much more needs to be learned about how to exploit these interactions. The design of screening strategies that probe targets in a holistic fashion is a critically important strategic element if new and unanticipated mechanisms of macromolecule modulation are to be uncovered. This is exemplified by the complex biochemical effects of **2**, which can only be assessed in a cell-based replicon system rather than a simple biochemical-based screen. Moreover, the increasing complexity and diversity of centamolecule structures is driving a demand for synthetic innovation in strategies, tactics, methodologies, capabilities, and decision making.[15] The tremendous burst of innovative advances in organic synthetic methodology that has occurred over the last 15 years, including developments in the application of radical chemistry, asymmetric catalysis, and fluorination technology, is helping to address this need.[15] These insights and advances are the result of a commitment to basic scientific research, an investment that, at a minimum, will need to be sustained if the growing demands of unmet medical needs are to be effectively addressed.[15,16]

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Notes

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ABBREVIATIONS

AIDS, acquired immunodeficiency syndrome; CA-SP1, capsid-spacer peptide 1junction; DAAs, direct-acting antiviral agents; FDA, Food and Drug Administration; GT, genotype; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus-1; LT, liver transplant; NASH, nonalcoholic steatohepatitis; NMEs, new molecular entities; PD, pharmacodynamic; SMA, spinal muscular atrophy; SMN, survival motor neuron; TP, thrombopoietin

REFERENCES

(1) Lichtenberg, F. R. The impact of biomedical innovation on longevity and health. *Nordic J. Health Econom.* **2017**, *5*, 45−57.

(2) Gottfried, J. *History Repeating? Avoiding a Return to the Pre-antibiotic Age*; Harvard Law School, Harvard University, April 17, 2005. Available at https://dash.harvard.edu/handle/1/8889467.

(3) Mullard, A. 2018 FDA drug approvals. *Nat. Rev. Drug Discovery* **2019**, *18*, 85−89.

(4) Centamolecules are those with molecular weights in the hundreds. See: Corey, E. J.; Baran, P. S. Short synthetic route to (+)-austamide, (+)-deoxyisoaustamide, and (+)-hydratoaustamide from a common precursor by a novel palladium-mediated indole → dihydroindoloazocine cyclization. *J. Am. Chem. Soc.* **2002**, *124*, 7904−7905.

(5) Lichtenberg, F. The effect of new drug approvals on HIV mortality in the US, 1987−1998. *Economics Human Biol.* **2003**, *1*, 259−266.

(6) Rein, D. B.; Wittenborn, J. S.; Weinbaum, C. M.; Sabin, M.; Smith, B. D.; Lesesne, S. B. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig. Liver Dis.* **2011**, *43*, 66−72.

(7) Flemming, J. A.; Kim, W. R.; Brosgart, C. L.; Terrault, N. A. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology* **2017**, *65*, 804−812.

(8) Belli, L. S.; Perricone, G.; Adam, R.; Cortesi, P. A.; Strazzabosco, M.; Facchetti, R.; Karam, V.; Salizzoni, M.; Andujar, R. L.; Fondevila, C.; De Simone, P.; Morelli, C.; Fabregat-Prous, J.; Samuel, D.; Agarwaal, K.; Moreno Gonzales, E.; Charco, R.; Zieniewicz, K.; De Carlis, L.; Duvoux, C. all the contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA). Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J. Hepatol.* **2018**, *69*, 810−817.

(9) Sun, J.-H.; O'Boyle, D. R., II; Fridell, R. A.; Langley, D. R.; Wang, C.; Roberts, S. B.; Nower, P.; Johnson, B. M.; Moulin, F.; Nophsker, M. J.; Wang, Y.-K.; Liu, M.; Rigat, K.; Tu, Y.; Hewawasam, P.; Kadow, J.; Meanwell, N. A.; Cockett, M.; Lemm, J. A.; Kramer, M.; Belema, M.; Gao, M. Resensitizing daclatasvir-resistant hepatitis C variants by allosteric modulation of NS5A. *Nature* **2015**, *527*, 245−258.

(10) Tonge, P. J. Drug-target kinetics in drug discovery. *ACS Chem. Neurosci.* **2018**, *9*, 29−39.

(11) Regueiro-Ren, A.; Dicker, I. B.; Hanumegowda, U.; Meanwell, N. A. Second generation inhibitors of HIV-1 maturation. *ACS Med. Chem. Lett.* **2019**, *10*, 287−294.

(12) Meanwell, N. A.; Krystal, M. R.; Nowicka-Sans, B.; Langley, D. R.; Conlon, D. A.; Eastgate, M. D.; Grasela, D. M.; Timmins, P.; Wang, T.; Kadow, J. F. Inhibitors of HIV-1 attachment: the discovery and development of temsavir and its prodrug fostemsavir. *J. Med. Chem.* **2018**, *61*, 62−80.

(13) Kuter, D. J. The biology of thrombopoietin and thrombopoietin receptor agonists. *Int. J. Hematol.* **2013**, *98*, 10−23.

(14) Shorrock, H. K.; Gillingwater, T. H.; Groen, E. J. N. Overview of current drugs and molecules in development for spinal muscular atrophy therapy. *Drugs* **2018**, *78*, 293−305.

(15) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018**, *10*, 383−394.

(16) Lindsley, C. W. Lost in translation: the death of basic science. *ACS Chem. Neurosci.* **2016**, *7*, 1024.

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ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX